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PHASE 4 CLINICAL STUDY PROTOCOL

An Exploratory Study of the Safety and Efficacy of Immune Tolerance Induction (ITI) in Patients with Pompe Disease Who Have Previously Received Myozyme

Protocol Number: AGLU03707
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Amendment 2: 19 March 2009
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Study Manager: [redacted]

Statistician: [redacted]

Safety Officer: [redacted]

Medical Monitor: [redacted]

Medical Monitor Signature Date

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in United States (US) federal regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

I have read and agree to abide by the requirements of this protocol.

Investigator Signature Date

1. SYNOPSIS

NAME OF COMPANY Genzyme Corporation 500 Kendall St. Cambridge, MA 02142 **NAME OF FINISHED PRODUCT** Myozyme® **NAME OF ACTIVE INGREDIENT** alglucosidase alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

TITLE: An Exploratory Study of the Safety and Efficacy of Immune Tolerance Induction (ITI) in Patients with Pompe Disease Who Have Previously Received Myozyme

PROTOCOL NO.: AGLU03707

INVESTIGATOR STUDY CENTERS: Up to 9 centers may participate in this study. Investigators overseeing this protocol and administering the agents in this regimen should be familiar with the medications administered, and preferably be an infectious disease expert and/or other specialist (such as an oncologist, immunologist, rheumatologist, or transplant specialist).

OBJECTIVES:

The objectives of the study are as follows:

1. To evaluate the efficacy of ITI regimens, as assessed by anti-recombinant human acid α-glucosidase (anti-rhGAA) antibody titers, and antibodies that inhibit the enzymatic activity and/or uptake of Myozyme;
2. To evaluate Pompe disease activity in patients receiving these regimens, as measured by overall survival, respiratory function, left ventricular mass index (LVMI), motor function, and disability index; and
3. To evaluate the safety of these regimens, as assessed by the incidence of adverse events (AEs), serious adverse events (SAEs), and clinical laboratory abnormalities.

METHODOLOGY:

This is an exploratory, open-label study of patients of any age with Pompe disease to evaluate the efficacy, safety, and clinical benefit of 2 ITI regimens in combination with Myozyme in patients receiving Myozyme treatment. The patient (and/or the patient's legal guardian[s] if the patient is <18 years of age) must provide written informed consent prior to any protocol-related procedure being performed. Eligible patients who are currently receiving Myozyme therapy will be enrolled into the study, and will be followed for a minimum of 18 months on-study (a 6-month ITI treatment module and a 12-month follow-up module on Myozyme alone). Eligible cross-reacting immunologic material (CRIM)-negative patients will be followed for a minimum of 18 months on treatment or, if a patient is <6 months of age at the time of enrollment, until the patient is 2 years of age.

Two ITI regimens will be evaluated in this protocol:

- Regimen A: Patients will be assigned to Regimen A if they exhibit clinical decline since starting Myozyme therapy and have inhibitory antibodies and/or a sustained high anti-rhGAA antibody titer (defined as at least 2 titers ≥25,600 obtained at least 1 month apart), regardless of their CRIM status. This regimen consists of a 6-month regimen of monthly cyclophosphamide.
- Regimen B: Only CRIM-negative patients are eligible to enroll in Regimen B. CRIM-negative patients will be assigned to Regimen B if they either (1) exhibit clinical decline since starting Myozyme therapy and do not have inhibitory antibodies or a sustained high anti-rhGAA antibody titer (defined as at least 2 titers ≥25,600 obtained at least 1 month apart), or (2) do not exhibit clinical decline since starting Myozyme therapy, regardless of their anti-rhGAA or

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inhibitory antibody status. Regimen B consists of a 4-week cycle of weekly rituximab in combination with a 6-month regimen of biweekly methotrexate. An optional, additional 4-week cycle of rituximab (up to 4 additional doses) may be administered within the first 6 months of the study, as described under **Dose/Route/Regimen**.

Patients on both regimens will receive intravenous (IV) infusions of Myozyme (20 mg/kg every other week (qow) for a minimum of 18 months or, if the patient is <6 months of age at the time of enrollment, until the patient is 2 years of age.

The treatment regimens are presented schematically under **Dose/Route/Regimen**.

Clinical decline for patients regardless of CRIM status will be defined as decline in at least 1 of the following parameters as compared to the condition of the patient prior to beginning Myozyme treatment:

Cardiac
Persistence of Left Ventricular Mass (LVM) Z-score ≥6 after a minimum of 6 months of treatment with Myozyme, OR

Respiratory
New development of respiratory failure requiring the use of ventilatory assistance (invasive or non-invasive) after a minimum of 6 months of treatment with Myozyme. Ventilatory assistance must have been required for at least 4 weeks prior to study enrollment, OR

Motor Skills
For patients ≤2 years of age at study entry, failure to acquire at least 2 new gross motor milestones or loss of at least 2 previously acquired gross motor milestones (or a combination thereof) after a minimum of 6 months of treatment with Myozyme, e.g.:

1. Turning head side to side (supine);
2. Grasping small objects with hands;
3. Transferring objects from hand to hand;
4. Holding head upright with body supported;
5. Rolling (supine to prone or prone to supine);
6. Sitting (supported or unsupported);
7. Walking (with support, i.e., cruising, or independently);
8. Walking up stairs (with assistance or independently); OR

Worsening of proximal upper extremity muscle weakness as determined by the Investigator through loss of functional use of the upper extremities after a minimum of 6 months of treatment with Myozyme; OR

Progression to use of an assistive device for ambulation due to worsening of proximal lower extremity muscle weakness after a minimum of 6 months of treatment with Myozyme.

Safety, efficacy, and exploratory evaluations will be performed at scheduled visits throughout the study as specified in the Schedule of Assessments. Ventilator use, AEs, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI/CTCAE), Version 3.0 (dated 09 August 2006), and concomitant and pre-infusion medications/therapies will be monitored continuously throughout the study.

An Immune Tolerance Induction Review Board (ITIRB) will evaluate the safety and efficacy of each of the ITI regimens after each patient completes 1 month of treatment on a given regimen, after each patient

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completes 6 months of treatment on a given regimen, and, if applicable, after the patient completes an optional, additional cycle of rituximab, as well as on an expedited *ad hoc* basis, as outlined in the ITIRB Charter (which is maintained separately from the protocol). The ITIRB will also provide recommendations about the risk/benefit profile of the ITI regimens. Should any safety concern arise, the final decision regarding the continuation of any or all patients in the study will be made by the Genzyme Global Patient Safety and Risk Management (GPS-RM) Safety Officer, or designee, and the ITIRB. If there are no major safety concerns, patients will continue to receive treatment in the study.

An independent Allergic Reaction Review Board (ARRB) will be consulted on an *ad hoc* basis, as outlined in the ARRB Charter (which is also maintained separately from the protocol). Should any major safety issues arise, the final decisions regarding the study will be made by the Genzyme GPS-RM Safety Officer, or designee, and the ARRB.

For consistency, a central cardiologist will review all electrocardiograms (ECGs) and echocardiograms (ECHOs).

Following study completion, patients may receive commercial Myozyme treatment as prescribed by their treating physicians. To facilitate long-term data collection, patients will be encouraged to enroll in the Pompe Disease Registry after study completion.

NUMBER OF SUBJECTS: It is planned that a total of 9 patients will initially be enrolled in the study. Patients will be assigned to either Regimen A or Regimen B based on their qualifications for a given regimen. Regimens will enroll as patients present until a total of 9 patients are treated. An attempt will be made to enroll a similar number of CRIM-positive and CRIM-negative patients on Regimen A, provided that sufficient number of qualified CRIM-negative patients can be identified within a reasonable study recruitment period. Enrollment will proceed in a sequential manner within each treatment regimen such that ITIRB review of data from the first patient within a regimen (for the first month of treatment) is completed prior to enrollment of any further patients on that regimen. If the regimen appears to have an acceptable risk/benefit profile after the first 3 patients in a given regimen have completed 1 month of treatment, additional patients may be enrolled as they present, or as necessary, to further evaluate the ITI regimen.

DIAGNOSIS/INCLUSION CRITERIA:
Inclusion Criteria:

1. The patient (and/or the patient's legal guardian(s) if the patient is <18 years of age) must provide written informed consent prior to any study-related procedures being performed;
2. The patient must have a clinical diagnosis of Pompe disease as defined by documented acid α-glucosidase (GAA) deficiency (deficient endogenous GAA activity) in skin fibroblasts, muscle, or blood, or presence of 2 GAA mutations. Consent will also be sought from the biological parent(s) for parental GAA mutational analysis, but is not a requirement for study eligibility;
3. The patient (and/or the patient's legal guardian(s) if the patient is <18 years of age) must have the ability to comply with the clinical protocol.
4. If the patient is CRIM-positive, he/she must have received Myozyme therapy (20 mg/kg qow) for at least 6 consecutive months immediately prior to enrollment in the study.
5. If the patient is CRIM-negative, he/she must have received at least 1 Myozyme infusion prior to

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enrollment in the study.

6. ***Regimen A only:***
   - The patient exhibits clinical decline (as defined under **Methodology**);
   - The patient has persistent high anti-rhGAA antibody titers (defined as at least 2 titers ≥25,600 obtained at least 1 month apart) and/or has tested positive for antibodies that inhibit enzymatic activity and/or uptake of Myozyme.

7. ***Regimen B only:***
   - The patient is CRIM-negative via Western blot analysis of skin fibroblasts; AND
   - The patient does NOT exhibit clinical decline (as defined under **Methodology**).

   OR

   - The patient is CRIM-negative via Western blot analysis of skin fibroblasts; AND
   - The patient exhibits clinical decline (as defined under **Methodology**); AND
   - The patient does NOT have persistent high anti-rhGAA antibody titers (defined as at least 2 titers ≥25,600 obtained at least 1 month apart) and has NOT tested positive for antibodies that inhibit enzymatic activity and/or uptake of Myozyme.

Note that historical CRIM testing results by Western blot analysis (performed prior to enrollment) are acceptable, provided that written documentation of the laboratory results is available at the enrolling site.

Exclusion Criteria:

1. The patient has any medical condition that, in the opinion of the Investigator, could interfere with the study regimens (i.e., Myozyme, cyclophosphamide, rituximab, and/or methotrexate) or assessments; such conditions may include, but are not limited to, active human immunodeficiency virus infection, cancer, or tuberculosis;
2. The patient is at risk of reactivation or is a carrier of Hepatitis B (e.g., Hepatitis B surface antigen is positive) or Hepatitis C (e.g., detectable Hepatitis C viral load by reverse transcriptase – polymerase chain reaction);
3. The patient is at risk of reactivation or has positive serology suggestive of active infection for cytomegalovirus (CMV), Herpes simplex, JC virus (progressive multifocal leukoencephalopathy), Parvovirus, or Epstein Barr virus;
4. The patient is at risk of reactivation of tuberculosis or has regular contact (e.g., in the household) with individuals who are being actively treated for tuberculosis;
5. The patient has low serum albumin, relative to institutional age-appropriate range, that is uncorrected;
6. The patient has a major congenital abnormality;
7. The patient has used any investigational product (other than Myozyme in those regions where the product is not commercially available and is considered investigational) within 30 days prior to study enrollment;
8. The patient is pregnant or lactating;

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9. The patient has had or is required to have any live vaccination within 1 month prior to enrollment.

At the discretion of the Investigator, clinical laboratory test results that are deemed to be due to transient illness may be repeated for the purpose of determining study eligibility.

DOSE/ROUTE/REGIMEN:

The treatments to be administered in this study are summarized below:

Patients on Regimen A

- Myozyme: 20 mg/kg IV qow for a minimum of 18 months or, if the patient is <6 months of age at the time of enrollment, until the patient is 2 years of age.
- Cyclophosphamide: 250 mg/ m^2 IV every 4 weeks after Myozyme infusion for 6 months.

The first 5 weeks of treatment for Regimen A are shown below.

	W1[a]	**W2[a]**	**W3[a]**	**W4[a]**	**W5[a]**
	D0	**D7**	**D14**	**D21**	**D28**
Myozyme	X		X		X
Cyclophosphamide[b]	X				X

[a] Weeks 2 to 5 will be repeated through Week 24 for Myozyme and cyclophosphamide AND from Week 25 to Week 75 for Myozyme.
[b] Refer to Table 9-1 of the study protocol for further guidance regarding the administration of cyclophosphamide.
Note: It is recommended that the Investigator monitor a patient's immunoglobulin levels and consider intravenous immunoglobulin (IVIG) administration at a dose of 400 mg/kg, regardless of age, if indicated per the individual Investigator's clinical discretion.
Key: W=Week; D=Day

Patients on Regimen B

- Myozyme: 20 mg/kg IV qow for a minimum of 18 months or, if the patient is <6 months of age at the time of enrollment, until the patient is 2 years of age.
- Rituximab: 375 mg/m^2 (or 12.5 mg/kg in those patients with a body surface area [BSA] ≤0.5 m^2) IV weekly for 4 weeks, beginning the day after the first Myozyme infusion. An optional, additional 4-week cycle of rituximab (up to 4 additional doses) may be administered within the first 6 months of the study. The administration of an additional cycle of rituximab must be discussed with and approved by the Genzyme GPS-RM Safety Officer, or designee, prior to implementation and may, at the discretion of Genzyme, also be reviewed with the ITIRB prior to implementation. This additional cycle must be completed within the first 6 months of the study. If the additional cycle is approved, these data will be included in the 6-month periodic ITIRB review. The total number of rituximab doses will not exceed 8 doses.
- Methotrexate: 15 mg/m^2 subcutaneous (SC) qow on the day after Myozyme infusion for 6 months. Folinic acid may be given at the discretion of the Investigator beginning 24 hours after the dose of methotrexate.

The first 6 weeks of treatment for Regimen B are shown below.

	W1	**W2**	**W3**	**W4**	**W5[a]**	**W6[a]**

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	D0	D1	D8	D14	D15	D22	D28	D29	D35
Myozyme	X			X			X		
Rituximab[b,c]		X	X		X	X			
Methotrexate[c]		X			X			X	

[a] Weeks 5 and 6 will be repeated through Week 24 for Myozyme and methotrexate AND from Week 25 to Week 75 for Myozyme.
[b] An optional, additional 4-week cycle of rituximab (up to 4 additional doses) may be administered as described above. This additional cycle must be completed within the first 6 months of the study.
[c] Refer to Table 9-2 of the study protocol for further guidance regarding the administration of rituximab and methotrexate.
Note: It is recommended that the Investigator monitor a patient's immunoglobulin levels and consider IVIG administration at a dose of 400 mg/kg, regardless of age, if indicated per the individual Investigator's clinical discretion.
Key: W=Week; D=Day

REFERENCE TREATMENT: Not applicable

CRITERIA FOR EVALUATION:

Efficacy: Efficacy will be assessed by anti-rhGAA antibody titers; the evaluation of inhibitory antibody formation (activity and uptake); overall survival; respiratory function as assessed by (a) the proportion of patients who were alive and ventilator-free over the course of treatment, time to overall invasive ventilator-dependence, and ventilator-free survival time for patients who were ventilator-free at the onset of the study, and (b) the overall duration of ventilator support and the number of hours of ventilator use in the 24 hours preceding each infusion visit for patients who required ventilator use at the onset of the study; LVMI as assessed by ECHO; and motor function and development as assessed by Gross Motor Function Measure-66, the Alberta Infantile Motor Scale, and the Pompe Pediatric Evaluation of Disability Inventory.

Safety: Safety will be evaluated in terms of AEs graded according to NCI/CTCAE, Version 3.0; vital sign parameters; physical examination findings; ECG parameters; routine laboratory measurements (hematology, chemistry, and urinalysis); lymphocyte subpopulations; an immunoglobulin panel; and pregnancy testing. Additional immunology measurements will include anti-rhGAA immunoglobulin E (IgE), serum tryptase, complement activation, and skin testing, when clinically indicated following moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or recurrent mild (Grade 1) infusion-associated reactions (IARs) to Myozyme that are suggestive of hypersensitivity; and circulating immune complex detection when clinically indicated by symptoms suggestive of immune complex disease.

Research immunophenotyping and functional T cell assays will also be performed as exploratory measures.

STATISTICAL METHODS:

Statistical analyses of all safety and efficacy measurements will be conducted on all patients who receive Myozyme under this protocol. All data will be presented in by patient listings. Graphical displays will be presented as appropriate. Summary statistics will be produced as appropriate and meaningful. Continuous variables will be summarized using descriptive statistics (number [n], mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequencies and percentages. No statistical testing will be conducted. Missing data will not be imputed using statistical methods.

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3. ABBREVIATIONS AND TERMS

Abbreviation	Definition
6MWT	6-Minute Walk Test
°C	Degrees Celsius
AE	Adverse event
AIMS	Alberta Infantile Motor Scale
anti-rhGAA	anti-recombinant human acid α-glucosidase
ARRB	Allergic Reaction Review Board
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CK	Creatine kinase
CK-MB	Creatine kinase-myocardial band
CMV	Cytomegalovirus
CPRS	Clinical Pharmacy Research Services
CRIM	Cross-reacting immunologic material
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ELISPOT	Enzyme-linked immunosorbent spot [assay]
EOS	End-of-Study
ERT	Enzyme replacement therapy
EU	European Union
FVC	Forced vital capacity
GAA	Acid α-glucosidase
GCP	Good Clinical Practice
GI	Gastrointestinal
GMAE	Gross Motor Ability Estimator
GMFM-66	Gross Motor Function Measure-66
GPS-RM	Global Patient Safety and Risk Management (formally Genzyme Pharmacovigilance)
HBV	Hepatitis B virus
HEENT	Head, Eyes, Ears, Nose, and Throat
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IAR	Infusion-associated reaction
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IND	Investigational New Drug [application]
IRB	Institutional Review Board
ITI	Immune tolerance induction
ITIRB	Immune Tolerance Induction Review Board
IV	Intravenous(ly)

Abbreviation	Definition
IVIG	Intravenous immunoglobulin
JRA	Juvenile rheumatoid arthritis
LSD	Lysosomal storage disorder
LVM	Left ventricular mass
LVMI	Left ventricular mass index
NCI/CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAIDs	Nonsteroidal anti-inflammatory drugs
PEDI	Pediatric Evaluation and Disability Inventory
PML	Progressive multifocal leukoencephalopathy (also known as JC Virus)
POR	Proof of Receipt
qow	Every other week
rhGAA	Recombinant human acid α-glucosidase
SAE	Serious adverse event
SC	Subcutaneous(ly)
SLE	Systemic lupus erythematosus
SOM	Study Operations Manual
US	United States

4. INTRODUCTION

4.1 Pompe Disease

Pompe disease is a rare, autosomal, recessive, metabolic muscle disease caused by the deficiency of acid α-glucosidase (GAA), an enzyme that degrades lysosomal glycogen. As opposed to the exclusively cytoplasmic accumulation of glycogen that occurs in other glycogen storage disorders, Pompe disease is characterized by organelle-bound (lysosomal) accumulation of glycogen in many body tissues, ultimately leading to multisystemic pathology.

Pompe disease is comprised of a broad spectrum of phenotypes ranging from a rapidly progressive form (infantile-onset) to a more slowly progressive form (late-onset), with considerable variability and overlap existing between these extremes (Chen, 2000, *Mol Med Today*; Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*; van den Hout, 2003, *Pediatrics*). It is important to note that all presentations of Pompe disease share a common underlying pathology (i.e., deficiency of GAA with subsequent accumulation of glycogen).

At the most rapidly progressive end of the disease spectrum, patients typically present with symptoms within the first 12 months of life. A massive deposition of glycogen in the heart and skeletal muscle results in rapidly progressive cardiomyopathy and generalized muscle weakness and hypotonia. Moreover, motor development is often completely arrested or, if motor milestones are achieved, they are subsequently lost. Death from cardiac and/or respiratory failure generally occurs before most patients reach 1 year of age (Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*).

At the other end of the spectrum, symptoms can appear during childhood or as late as the sixth decade of life and progress less rapidly but relentlessly. Patients present with progressive myopathy, predominantly of the proximal muscles in the pelvic and shoulder girdles, and a variable progression of respiratory involvement. Typically these patients develop minimal or no cardiomyopathy (Chen, 2000, *Mol Med Today*; Laforêt, 2000, *Neurology*; Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*). Pompe disease presenting in older children and adults is less predictable than in infants, with some patients experiencing a rapid deterioration in skeletal and respiratory muscle function leading to loss of ambulation and respiratory failure, others progressing less rapidly, and yet others with dissociation in the progression of skeletal and respiratory muscle involvement (Laforêt, 2000, *Neurology*). Eventually, most patients become wheelchair-bound, require ventilator support, and ultimately succumb to respiratory failure (Chen, 2000, *Mol Med Today*; Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*).

4.2 Myozyme

Myozyme® (alglucosidase alfa) is indicated for use in patients with Pompe disease. Myozyme has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas use of Myozyme in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy. The recommended dosage regimen of Myozyme is 20 mg/kg body weight administered every other week (qow) as an intravenous (IV) infusion. Genzyme Corporation has also successfully developed enzyme replacement therapy (ERT) for the treatment of 3 other lysosomal storage disorders (LSDs) – Gaucher disease, Fabry disease, and mucopolysaccharidosis type 1 – which, like Pompe disease, are characterized by accumulation of enzyme substrate in a variety of tissues resulting in multisystemic pathology (Barton, 1991, *N Engl J Med*; Eng, 2001, *N Engl J Med*; Kakkis, 2001, *N Engl J Med*).

In this study, AGLU03707, Myozyme will be given at the recommended dose of 20 mg/kg qow as an approximately 4-hour infusion for a minimum of 18 months or until the patient is 2 years of age, whichever is longer. The safety and efficacy of the recommended dose (and higher doses) of Myozyme has been evaluated in 3 clinical studies with patients naïve to ERT at initiation of treatment. In addition, several other studies and expanded access programs were conducted which also evaluated safety and efficacy. Key findings from the 3 aforementioned Good Clinical Practice (GCP) studies are detailed below; additional efficacy data from these and other studies may be found in the current Myozyme Investigator's Brochure. Specific information on the risks associated with Myozyme treatment is provided below in Section 4.4.1 and in the Myozyme Investigator's Brochure.

Two of these studies (AGLU01602/AGLU02403, AGLU01702) were conducted in patients with infantile-onset disease. In these patients, Myozyme markedly extended survival and prevented or delayed time to ventilator dependence as compared with an untreated historical cohort. Myozyme also reversed indices of cardiomyopathy. Moreover, consistent gains in motor function were observed, with a subset of patients achieving independent ambulation. These findings contrast sharply with the severe and unremitting clinical deterioration observed in virtually all untreated patients with infantile-onset Pompe disease (van den Hout, 2003, *Pediatrics*).

In older children with Pompe disease (AGLU02804), Myozyme was associated with maintenance or improvements in pulmonary function, muscle strength, gross motor function, and functional status/disability. These results are in sharp contrast to the progressive nature of late-onset Pompe disease in untreated patients (Laforêt, 2000, *Neurology;* Hagemans, 2005, *Neurology;* Hagemans, 2005, *Brain*; Winkel, 2005, *J Neurol*).

4.2.1 AGLU01602/AGLU02403

The pivotal study, AGLU01602, was an international, multicenter, historically controlled clinical study of 18 patients presenting with Pompe disease as infants and who were age 7 months or less at first Myozyme infusion and were not ventilated. Patients were randomized equally to receive either 20 mg/kg or 40 mg/kg Myozyme qow, with length of treatment ranging from 52 to 106 weeks. The primary endpoint was the proportion of patients alive and free of invasive ventilation at 18 months of age (time to event) with an untreated historical cohort derived from a retrospective natural history study (n=62) serving as a comparator group. At the 18-month milestone age, 15 (83%) of the 18 patients were alive and free of invasive ventilation (3 patients were alive but invasively ventilated). In contrast, only 2% of cases in the untreated historical cohort survived by age 18 months. At the end of Study AGLU01602, 17 of the 18 treated patients were alive; 1 patient required invasive ventilation at 19.4 months and later died from desaturation and bradycardia (unrelated to Myozyme) at 19.8 months of age. Sixteen of the 17 surviving patients went on to receive Myozyme treatment in an approximately 12-month extension study (AGLU02403). The remaining patient continued to receive treatment with Myozyme via the international expanded access program at a center near the patient's home and subsequently died of multi-organ failure secondary to septicemia (unrelated to Myozyme). At the end of Study AGLU02403, 14 (77.8%) of the 18 patients initially treated in AGLU01602 were alive. The 2 patients who died in AGLU02403 were invasively ventilated at the time of death; cause of death in both patients was cardiorespiratory arrest assessed as unrelated to treatment with Myozyme.

4.2.2 AGLU01702

Study AGLU01702 was an international, multicenter, open-label clinical study of 21 patients presenting with Pompe disease as infants and who were >6 months to 3 years of age at first Myozyme treatment. All patients received 20 mg/kg Myozyme qow. Five of 21 patients were receiving invasive ventilator support at the time of first infusion. The primary outcome measure was the proportion of patients alive at the conclusion of treatment. At the 52-week interim analysis, 16 of 21 patients were alive, yielding a 52-week survival rate of 76%, as compared with a 52-week survival rate of 31.6% in an untreated historical reference subgroup. In addition, treatment with Myozyme for 52 weeks under AGLU01702 prevented ventilator dependence in 10 of the 16 patients who were invasive ventilator-free at Baseline. As of the end of the study (up to approximately 39 months on treatment), 15 (71.4%) patients were alive. The age range of the 15 surviving patients was from 34.7 to 80.3 months. In the remaining 6 treated patients who died, cause of death was consistent with cardiac and respiratory complications of underlying Pompe disease; none of the deaths was assessed as related to treatment with Myozyme.

4.2.3 AGLU02804

AGLU02804 was a single-center, open-label clinical study that assessed the efficacy of Myozyme in 5 patients with late-onset Pompe disease, who ranged in age from 5 to 15 years at initiation of treatment. Patients received 20 mg/kg Myozyme qow for 26 weeks. All patients were ambulatory at baseline and 4 of 5 patients did not require any form of ventilator support (1 patient required nocturnal non-invasive ventilation). Of the 3 patients with significant pulmonary involvement at baseline (percentage predicted forced vital capacity [FVC] in the sitting position <80%), 2 demonstrated clinically meaningful improvements in FVC (>11%) in the sitting position by Week 26. Evaluation of motor function was evaluated using the 6-Minute Walk Test (6MWT). Three of the patients demonstrated a clinically meaningful improvement (>37 m difference) in the 6MWT at fast speed by Week 26.

4.3 Immune Tolerance Induction

The majority of patients (approximately 90%) in clinical studies developed immunoglobulin G (IgG) antibodies to Myozyme, typically within 3 months of initiating Myozyme treatment (see Section 4.4.1.7, Immunogenicity, for further details). Currently, the effect of antibody development on the long-term efficacy of Myozyme is not fully understood. There is an observation that some patients who develop high and sustained anti-Myozyme antibody titers also exhibit a poorer clinical response to treatment. The causes leading to the poor clinical response to Myozyme treatment in these and other patients are thought to be multi-factorial. One strategy for potentially improving clinical outcome in patients receiving Myozyme may be to administer an immune tolerance induction (ITI) regimen, either before or after recombinant human acid α-glucosidase (rhGAA) antibodies and/or inhibitory antibodies have been detected.

The timing of administration of such an ITI regimen will depend upon the risk:benefit ratio to the patient. Patients with early onset of symptoms of Pompe disease (infantile-onset) may be at increased risk of developing anti-recombinant human acid α-glucosidase (anti-rhGAA) antibodies that affect efficacy due to the higher frequency of fully deleterious (null) mutations resulting in GAA protein absence (cross-reacting immunologic material [CRIM]-negative). Therefore, patients who are CRIM-negative may benefit most from prophylactic ITI treatment, i.e., an ITI regimen that is administered prior to the patient exhibiting any evidence of clinical decline. In contrast, patients with less deleterious mutations (in at least 1 of 2 disease alleles) that result in defective but present endogenous GAA protein (CRIM-positive) may be at lower risk of antibody interference. Therefore, given the potential risks of ITI treatment, for CRIM-positive patients it may be more prudent to begin an ITI regimen only if a patient exhibits evidence of clinical decline in association with the development of inhibitory antibodies or a sustained, high anti-rhGAA titer. CRIM-negative patients who already exhibit clinical decline may also benefit from ITI treatment under these conditions, if the clinical decline is thought to be

the result of antibody interference. In CRIM-negative patients who already present with clinical decline and inhibitory antibodies or high anti-rhGAA titer, a more aggressive ITI regimen may be warranted to achieve a significant reduction in antibody titer that may lead to clinical improvement. Due to the increased risk for CRIM-negative patients to develop inhibitory antibodies or high anti-rhGAA titer, Genzyme is conducting a separate study (AGLU03807) to explore the effects of ITI in Myozyme-naïve CRIM-negative patients.

There are few systematically collected data assessing ITI strategies for patients with LSDs in general, and in Pompe disease in particular. Nevertheless, the potential serious consequence of antibody interference with the efficacy of Myozyme in patients with Pompe disease warrants consideration of therapeutic intervention with highly experimental ITI regimens. It is hypothesized that prevention or significant reduction of antibody formation may minimize the clinical impact of antibodies on treatment outcomes while allowing continued treatment with Myozyme.

The development of an ITI protocol for this Pompe patient population is challenging. Relevant clinical precedent was primarily established in diseases such as hemophilia, which is not directly comparable to Pompe disease. For example, hemophiliac patients are deficient in a secreted plasma protein while Pompe patients are deficient in an intracellular catabolic enzyme, which is mostly secluded in the lysosome. Also, the presence of cardiac disease and respiratory insufficiency in the Pompe disease population adds a risk of potential cardiopulmonary complications due to immunotherapy that is usually not a concern for patients with hemophilia.

Experience with the use of ITI regimens in other LSDs has shown that a total dose increase and change from biweekly to weekly infusions of ERT was successful for 2 patients with Gaucher disease who exhibited limited clinical benefit and inhibitory antibody development, as reported in the literature (Zhao, 2003, *Blood Cells Mol Dis*; Ponce, 1997, *Blood*). A third patient with type 3 Gaucher disease successfully underwent ITI with a combination of increased dose of ERT and a 10-day cyclophosphamide regimen, including plasmapheresis on days 1, 3 and 5, and administration of intravenous immunoglobulin (IVIG) on days 5 to 10, as well as low-dose, oral cyclophosphamide for up to 30 days (Brady, 1997, *Pediatrics*).

There also has been limited experience with the use of ITI regimens in Pompe disease. Two CRIM-negative infants who received an earlier form of rhGAA (Synpac rhGAA under Investigational New Drug [IND] application 8324; different from Myozyme) developed high, sustained anti-rhGAA IgG titers and underwent unsuccessful experimental ITI on an ITI regimen similar to that described by Brady et al (Brady, 1997, *Pediatrics*). In addition, 1 of these patients also received a total of 6 doses of Rituxan® (rituximab) in a subsequent, also unsuccessful, ITI regimen attempt (Genzyme Study GAA-CL-002). In both patients, the ITI regimens proved

ineffective, as any reduction in anti-rhGAA antibody levels was transient. Both patients experienced bacterial and viral infections during the ITI regimen; these infections were considered by the treating physicians to be possibly due to a weakened immune system. One patient developed nephrotic syndrome secondary to immune complex formation while receiving high-dose Synpac rhGAA administered 5 times weekly; the onset of nephrotic syndrome occurred after the patient had discontinued the ITI regimen (Hunley, 2004, *Pediatrics*).

Through a series of preclinical studies in GAA knockout mice, which exhibit an rhGAA-specific antibody response following treatment with rhGAA, a potential regimen for a short course of immunotherapy to induce long-term immune tolerance to Myozyme has been developed (Genzyme Study ITR-333-1106). The regimen in GAA knockout mice involved prophylactic administration of three 3-day courses of intraperitoneal methotrexate, given around the first 3 or 8 weekly infusions of Myozyme, and was based on previous experiments performed at Genzyme in a GAA knockout mouse model, in which the murine a-glucosidase gene has been disrupted through insertion of the neomycin phosphotransferase gene in exon 6 ($6^{neo}/6^{neo}$), as reported by Raben et al (Raben, 1998, *J Biol Chem*). This regimen, when administered at doses of 0.5 mg/kg and 5.0 mg/kg, was found to consistently reduce the antibody levels in GAA knockout mice over at least 8 months, although variability was higher at the lower dose. Notably, a number of unsuccessful therapeutic options were also tested in the GAA knockout mouse model, which included mycophenolate mofetil, cyclosporine A plus azathioprine, cytotoxic T-lymphocyte antigen 4-Ig fusion protein, and anti-thymocyte globulin.

This exploratory clinical study (AGLU03707) will employ 2 clinical ITI regimens to determine whether this regimen can reduce the immunogenicity of Myozyme in patients with Pompe disease. The first regimen (Regimen A) will involve administration of monthly IV cyclophosphamide for 6 months. The second regimen (Regimen B) is similar to that used to induce immune tolerance in GAA knockout mice, and will consist of administration of biweekly subcutaneous (SC) methotrexate for 6 months, with the addition of a 4-week cycle of weekly IV rituximab to aid in decreasing long-term antibody production against Myozyme. These immunosuppressant agents (cyclophosphamide, rituximab, and methotrexate) were considered because reports exist for use in children (and cyclophosphamide and methotrexate are both approved for specific indications in children), and these agents have been used successfully to treat diseases with an important immunologic component such as systemic lupus erythematosus (SLE) and juvenile rheumatoid arthritis (JRA), including cases where other therapies have failed, although the specific mechanism of action of these agents in the treatment of pediatric SLE and JRA are not known. Cyclophosphamide is proposed for patients already demonstrating high antibody titers and/or *in vitro* inhibitory antibodies along with evidence of clinical decline, and was chosen primarily because of its rapid onset of action and potency based on limited

information in children with immune diseases (primarily SLE and JRA, as described above). In CRIM-negative patients who do not yet demonstrate high antibody titers, inhibitory antibodies, or evidence of clinical decline, a regimen consisting of weekly rituximab and biweekly methotrexate is proposed because there may be less acute toxicity with this regimen, and it may therefore be more appropriate for a population where there is no immediate need to reduce antibody titer.

It is recommended that the Investigator monitor a patient's immunoglobulin levels and consider IVIG administration, regardless of age, if indicated per the individual Investigator's clinical discretion.

The development of antibody titers in patients treated with Myozyme points towards a role of the B cell compartment component in immunological response; however, the role of the T cell compartment in patients with Pompe disease has not been previously evaluated. Therefore, in conjunction with administration of an ITI regimen in this study, laboratory assessments will be performed to study the contribution of the T cell compartment to the immune response against Myozyme. Genzyme will also investigate the correlation among genotype, the level of α-glucosidase protein, and the presence of binding, anti-rhGAA IgG, and inhibitory antibodies over time, using validated assays.

4.3.1 Cyclophosphamide

In this study, cyclophosphamide will be given as an investigative, off-label agent at the dose of 250 mg/m^2 IV every 4 weeks for a total of 6 months, with each dose being administered after completion of a Myozyme infusion.

Cyclophosphamide is an immunosuppressive agent that is biotransformed (principally in the liver) to active alkylating metabolites that interfere with the growth of susceptible rapidly proliferating malignant cells, presumably through a mechanism of action that involves cross-linking of tumor cell deoxyribonucleic acid (DNA). Cyclophosphamide is approved for the treatment of various malignancies and nephrotic syndrome in children. Cyclophosphamide has also been used to treat autoimmune diseases such as pediatric SLE and JRA, with conventional therapy typically involving monthly IV doses of 500 to 1000 mg/m^2.

Further details on the potential risks of cyclophosphamide are provided in Section 4.4.2.1. A full description of cyclophosphamide is available in the local prescribing information. The United States (US) prescribing information is provided as an appendix to this protocol (Appendix 14.1); additional countries should refer to their local authorities' approved prescribing information. Investigators should familiarize themselves with any relevant premedication requirements, contraindications, warnings, precautions for use, and the adverse event (AE) profile provided therein.

4.3.2 Rituximab

In this study, rituximab will be given as an investigative, off-label agent at the recommended dose of 375 mg/m^2 (or 12.5 mg/kg in those patients with a body surface area [BSA] ≤0.5 m^2) IV infusion once weekly for 4 doses, with the first rituximab infusion occurring on the day after the first Myozyme infusion in this study. A patient who completes the initial cycle of rituximab treatment may be considered for an optional, additional 4-week cycle of rituximab (up to 4 additional doses) within the first 6 months of the study, as described in Section 8.1. The total number of weekly 375 mg/m^2 IV infusions of rituximab will not exceed 8 doses.

Rituximab is a chimeric anti-CD20 monoclonal antibody designed to target the CD20 antigen, which is a transmembrane protein expressed on >90% of all B cell non-Hodgkin's lymphomas. CD20 expression is restricted to B cell precursors and mature B cells, and is not found in plasma cells (or other normal tissues). Rituximab is approved for the treatment of non-Hodgkin's lymphoma and rheumatoid arthritis. Rituximab is a liquid concentrate intended for IV administration via a dedicated line.

In 14 patients given rituximab 375 mg/m^2 as an IV infusion for 4 weekly doses, the mean serum half-life was 76.3 hours (range 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range 83.9 to 407.0 hours) after the fourth infusion. The wide range of half-lives may reflect the variable tumor burden among patients and changes in CD20-positive (normal and malignant) B-cell populations upon repeated administrations.

Further details on the potential risks of rituximab are provided in Section 4.4.2.2. A full description of rituximab is available in the local prescribing information. The US prescribing information is provided as an appendix to this protocol (Appendix 14.2); additional countries should refer to their local authorities' approved prescribing information. Investigators should familiarize themselves with any relevant premedication requirements, contraindications, warnings, precautions for use, and the AE profile provided therein.

4.3.3 Methotrexate

In this study, methotrexate will be administered as an investigative off-label agent qow at a dose of 15 mg/m^2, administered as an SC injection on the day after Myozyme infusion for the first 6 months of treatment. This dose of methotrexate is approximately 1.8-fold higher than the human equivalent of the lowest effective dose in the GAA knockout mouse studies, when accounting for species differences and frequency of methotrexate administration in AGLU03707 and GAA knockout mouse studies. Of note, this does not take into account the difference in route of administration between that proposed in AGLU03707 and that used in GAA knockout mouse studies.

Methotrexate is an anti-metabolite agent that acts by inhibiting dihydrofolate reductase (an enzyme required for cell division). Methotrexate is approved for the treatment of cancer of the breast, head and neck, lung, stomach, and esophagus, as well as gestational trophoblastic cancer, sarcomas, non-Hodgkin's lymphoma, psoriasis, rheumatoid arthritis, and Crohn's disease. To date, the safety and effectiveness of methotrexate for a pediatric population has been established for its use as therapy for cancer and polyarticular-course JRA.

Methotrexate will be administered SC in this study, as experience in the treatment of polyarticular-course JRA suggests that children receiving 20 to 30 mg/m^2/week may have better absorption and fewer gastrointestinal (GI) side effects if methotrexate is administered either intramuscularly or SC. Folinic acid may be given at the discretion of the Investigator beginning 24 hours after the dose of methotrexate.

Further details on the potential risks of methotrexate are provided in Section 4.4.2.3. A full description of methotrexate is available in the local prescribing information. The US prescribing information is provided as an appendix to this protocol (Appendix 14.3); additional countries should refer to their local authorities' approved prescribing information. Investigators should familiarize themselves with any relevant premedication requirements, contraindications, warnings, precautions for use, and the AE profile provided therein.

4.3.4 Intravenous Immunoglobulin

It is recommended that the Investigator monitor a patient's immunoglobulin levels and consider IVIG administration at a dose of 400 mg/kg, regardless of age, if indicated per the individual Investigator's clinical discretion. The US prescribing information is provided as an appendix to this protocol (Appendix 14.4).

There are no published data regarding IVIG prophylaxis in this setting.

4.4 Risks

4.4.1 Risks Associated With Myozyme (alglucosidase alfa)

Refer to the current Investigator's Brochure and local prescribing information for further details concerning clinical experience with Myozyme.

4.4.1.1 Anaphylaxis and Allergic Reactions

Life-threatening anaphylactic reactions, including anaphylactic shock, have been observed in patients during Myozyme infusions. Because of the potential for severe infusion reactions, appropriate medical support measures should be available when Myozyme is administered.

If anaphylactic or other severe allergic reactions occur, immediate discontinuation of the administration of Myozyme should be considered, and appropriate medical treatment should be initiated.

The risks and benefits of re-administering Myozyme following an anaphylactic or severe allergic reaction should be considered. Some patients have been rechallenged and have continued to receive Myozyme under close clinical supervision. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product. Refer to the local prescribing information and the Investigator's Brochure for additional details on the risks of anaphylactic and allergic reactions.

4.4.1.2 Acute Cardiorespiratory Failure

Acute cardiorespiratory failure requiring intubation and inotropic support has been observed up to 72 hours after infusion with Myozyme in infantile-onset Pompe disease patients with underlying cardiac hypertrophy, possibly associated with fluid overload with IV administration of Myozyme. Patients with an acute illness at the time of Myozyme infusion may be at greater risk for experiencing acute cardiorespiratory failure. Infants with cardiac dysfunction may require prolonged observation times that should be individualized based on the needs of the patient.

4.4.1.3 Cardiac Arrhythmia and Sudden Cardiac Death During General Anesthesia for Central Catheter Placement

A central venous catheter may be inserted for this study, at the discretion of the Investigator. Caution should be used when administering general anesthesia for the placement of a central venous catheter or for other surgical procedures in infantile-onset Pompe disease patients with cardiac hypertrophy.

Cardiac arrhythmia, including ventricular fibrillation, ventricular tachycardia and bradycardia, resulting in cardiac arrest or death, or requiring cardiac resuscitation or defibrillation have been observed in infantile-onset Pompe disease patients with cardiac hypertrophy, associated with the use of general anesthesia for the placement of a central venous catheter intended for Myozyme infusion (Ing, 2004, *Paediatr Anaesth*).

4.4.1.4 Infusion-Associated Reactions

An infusion-associated reaction (IAR) is a sub-category of AEs used only in relationship to Myozyme. IARs were defined as AEs that occurred during either the Myozyme infusion or the observation period following the infusion which were deemed to be related (i.e., possibly, probably or definitely) to study drug. At the discretion of the Investigator, AEs that occurred after completion of the post-infusion observation period that were assessed as related could also

be considered IARs. IARs occurred in approximately 50% of patients treated for 52 weeks with Myozyme in 2 clinical studies of infantile-onset disease. IARs occur at any time during, and mostly up to 2 hours after the infusion of Myozyme, and are more likely with higher infusion rates and have occurred in some patients after receiving antipyretics, antihistamines, or steroids. Patients with an acute illness at the time of Myozyme infusion may also be at greater risk for IARs. The majority of IARs were assessed as mild to moderate; some reactions were severe. Refer to the current Investigator's Brochure and local prescribing information for important safety information on IARs' management.

4.4.1.5 Immune-Mediated Reactions

Severe cutaneous and systemic immune mediated reactions have been reported in postmarketing safety experience with Myozyme in at least 2 patients, including ulcerative and necrotizing skin lesions, and possible type III immune complex-mediated reactions. These reactions occurred several weeks to 3 years after initiation of Myozyme infusions. Skin biopsy in 1 patient demonstrated deposition of anti-rhGAA antibodies in the lesion. Another patient developed severe inflammatory arthropathy in association with fever and elevated erythrocyte sedimentation rate. Patients should be monitored for the development of systemic immune complex-mediated reactions involving skin and other organs while receiving Myozyme.

4.4.1.6 Adverse Events

While most patients experienced AEs, the majority of AEs were mild or moderate in severity and assessed as unrelated to treatment. Most serious adverse events (SAEs) experienced by patients were also mild or moderate in severity and assessed as unrelated to treatment and were respiratory, cardiac, or infectious in nature. The majority of SAEs and AEs were not unexpected given the multi-systemic nature or advanced stage of Pompe disease.

4.4.1.7 Immunogenicity

The majority of patients (approximately 90%) in 2 clinical studies of infantile-onset disease tested positive for IgG antibodies to Myozyme. The data reflect the percentage of patients whose test results were considered positive for antibodies to Myozyme using an enzyme-linked immunosorbent assay and radioimmunoprecipitation assay for Myozyme-specific IgG antibodies. Most patients who develop antibodies do so within the first 3 months of exposure.

Patients in clinical trials, expanded access programs, and on commercial therapy have undergone testing for Myozyme-specific immunoglobulin E (IgE) antibodies. Testing was performed for IARs, especially moderate to severe or recurrent reactions, for which mast-cell activation was suspected. A small number of these patients tested positive for Myozyme-specific IgE antibodies, some of whom experienced an anaphylactic reaction. Some patients have been

successfully rechallenged and continued to receive treatment with Myozyme under close clinical supervision.

It is therefore recommended that patients treated with Myozyme undergo antibody testing at least every 3 months and that those who experience a decrease in clinical benefit despite adhering to the recommended dosing regimen be tested for inhibition of enzyme uptake or activity by an *in vitro* assay. In the current AGLU03707 study, more frequent monitoring of anti-rhGAA IgG titer will be performed to fully evaluate the antibody response during and following treatment with immunosuppressants.

4.4.2 Risks Associated With Immune Tolerance Induction (ITI)

ITI requires the use of agents that may cause additional complications (such as recurrent infections) that could be fatal for critically ill patients with Pompe disease. For these reasons, Genzyme recommends that careful consideration of the risks and benefits for the individual patient be given and that investigators overseeing this protocol and administering the agents in this regimen should be familiar with the medications administered, and preferably be an infectious disease expert and/or other specialist (such as an oncologist, immunologist, rheumatologist, or transplant specialist).

As discussed in detail in Section 4.4.2.1, Section 4.4.2.2 and Section 4.4.2.3, respectively, cyclophosphamide, rituximab, and methotrexate can have direct toxicities. As there are no controlled studies using these agents in patients with Pompe disease or other patients <2 years of age who have diseases other than Pompe, the toxicities are unknown. Furthermore, the proposed treatment combinations of Myozyme with cyclophosphamide, rituximab, and/or methotrexate have not been used, and the combination of agents could have broader side effects than those observed with the individual agents. During this study, patients should be closely monitored for any signs of toxicity, including monitoring for any changes in serum creatinine, blood urea nitrogen (BUN), platelets, white cell count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, the presence of red cells in the urine, as well as any clinical symptoms of renal, hepatic, bone marrow, or pulmonary toxicity. Potentially confounding factors include the frequent elevation of ALT, AST, creatine kinase (CK), and creatine kinase-myocardial band (CK-MB) (secondary to muscle cell damage) and respiratory complications in patients with Pompe disease.

Immunosuppression can also result in opportunistic infections such as *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*) pneumonia as well as other common and opportunistic bacterial, fungal, and viral infections. Patients with Pompe disease may be at increased risk of such infections due to the progressive effects of the disease on the respiratory muscles. In the AGLU03707 study, precautions must be taken to prevent the transmission of infection, and

infection prophylaxis for *P. jiroveci* is recommended. Patients should be monitored closely for any sign of infection during the study, with consequent aggressive treatment and management if this should occur. In selecting an antibiotic to treat the infection, attention should be given to potential drug interactions among the investigative agents and certain antibiotics. It is also recommended that an infectious disease specialist be consulted whenever any antimicrobial agent is to be administered for the treatment of active infection in patients receiving the ITI regimen. Further detail on supportive measures for prophylaxis, monitoring, and treatment of infections are provided in Section 8.3, and in the Study Operations Manual (SOM).

Vaccination with live virus is not recommended in immunosuppressed children. Therefore, in the AGLU03707 study, vaccination with live virus will be prohibited within 1 month prior to enrollment in this study and until a patient's B cell count returns to normal or at least 3 months following completion of the ITI regimen, whichever is longer. The effectiveness of inactive virus given concomitantly with the immunosuppressant agents in this study is questionable. However, patients undergoing ITI regimens may benefit from specific immunizations directed at preventing infections by organisms to which they are particularly susceptible, e.g., pneumococcal, influenza, and/or meningococcal vaccines. Further detail is provided in Section 8.3, and in the SOM.

Adjustment to a patient's ITI regimen may be made in consultation with Genzyme (and the Immune Tolerance Induction Review Board [ITIRB], as appropriate) if medically indicated, in an effort to allow the patient to safely continue in the study while maintaining the potential clinical benefit of the regimen. If severe toxicity or infection should occur (see Section 7.3.2), the patient will be temporarily withdrawn from the ITI regimen until further evaluation, and the regimen may be permanently discontinued pending the outcome of that evaluation. The Investigator may also withdraw the patient from the regimen at any time, if he/she considers this to be in the best interest of the patient.

4.4.2.1 Risks Associated With Cyclophosphamide

A full description of cyclophosphamide, any relevant premedication requirements, contraindications, warnings, precautions for use, and the AE profile, as well as preparation instructions, is in the local prescribing information (refer to Appendix 14.1). Investigators are requested to adhere to recommendations provided therein. A summary of boxed warnings and contraindications relevant to this patient population is provided directly below.

Cyclophosphamide is contraindicated in patients who develop severely depressed bone marrow function.

Serious, sometimes fatal, infections may develop in severely immunosuppressed patients. Cyclophosphamide treatment may not be indicated, or should be interrupted, or the dose reduced, in patients who have or who develop viral, bacterial, fungal, protozoan, or helminthic infections.

Secondary malignancies have developed in some patients treated with cyclophosphamide alone or in combination with other agents, and most frequently in patients treated for primary myeloproliferative or lymphoproliferative malignancies or nonmalignant disease in which immune processes are believed to be involved pathologically.

Cyclophosphamide interferes with oogenesis and spermatogenesis, and may cause sterility in both sexes; sterility may be irreversible in some patients. Amenorrhea associated with decreased estrogen and increased gonadotropin secretion develops in a significant proportion of women treated with cyclophosphamide; affected patients generally resume regular menses within a few months after cessation of therapy. Men treated with cyclophosphamide may develop oligospermia or azoospermia associated with increased gonadotropin but normal testosterone secretion; azoospermia is reversible in some patients, though the reversibility may not occur for several years after cessation of therapy.

Cyclophosphamide can also cause fetal harm when administered to a pregnant woman, with reported fetal abnormalities including ectrodactylia. Women of childbearing potential should be advised to avoid becoming pregnant. If a patient should become pregnant while taking cyclophosphamide, that patient should be appraised of the potential hazard to the fetus.

Hemorrhagic cystitis may develop in patients treated with cyclophosphamide; in rare instances this can be severe and even fatal. Fibrosis of the urinary bladder, sometimes extensive, also may develop with or without accompanying cystitis. Atypical urinary bladder epithelial cells may appear in the urine. These adverse effects appear to depend upon the dose of cyclophosphamide and the duration of therapy. Such bladder injury is thought to be due to cyclophosphamide metabolites excreted in the urine. Forced fluid intake helps to assure an ample output of urine, necessitates frequent voiding, and reduces the time the drug remains in the bladder. Hematuria usually resolves in a few days after cyclophosphamide treatment is stopped, but it may persist. Medical and/or surgical supportive treatment may be required, rarely, to treat protracted cases of severe hemorrhagic cystitis. It is usually necessary to discontinue cyclophosphamide therapy in instances of severe hemorrhagic cystitis. In the current study, patients should be well hydrated prior to cyclophosphamide infusion (taking into account the proper hydration given the patient's cardiac status) and monitored regularly for the presence of red cells in the urine, which may precede hemorrhagic cystitis.

Although a few instances of cardiac dysfunction have been reported following use of recommended doses of cyclophosphamide, no causal relationship has been established. Acute

cardiac toxicity has been reported with doses as low as 2.4 gram/m^2 (usually as a portion of an intensive antineoplastic multidrug regimen or in conjunction with transplantation procedures) and, in a few instances, severe and sometimes fatal congestive heart failure has occurred after the first dose of a high-dose cyclophosphamide regimen.

Anaphylactic reactions have been reported; death has also been reported in association with this event. Possible cross-sensitivity with other alkylating agents has been reported.

Cyclophosphamide treatment, which causes a marked and persistent inhibition of cholinesterase activity, potentiates the effect of succinylcholine chloride. If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted.

4.4.2.2 Risks Associated With Rituximab

A full description of rituximab, any relevant premedication requirements, contraindications, warnings, precautions for use, and the AE profile, as well as preparation instructions, is in the local prescribing information (refer to Appendix 14.2). Investigators are requested to adhere to recommendations provided therein. A summary of boxed warnings and contraindications relevant to this patient population is provided directly below.

Deaths have been reported within 24 hours of infusion with rituximab. These fatal infusion reactions followed an infusion reaction complex, which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred with the first infusion. Therefore, in the current study, all rituximab infusions will be administered in a hospital setting with appropriate emergency care facilities.

Severe mucocutaneous reactions, some fatal, have been reported with rituximab. These include Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in the reported cases has varied from 1 to 13 weeks following rituximab exposure. Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and should receive prompt medical evaluation.

Rituximab is contraindicated for patients with known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of the product.

Patients with pre-existing cardiac conditions have had recurrences of these events during rituximab therapy. To manage these risks in the current study, continuous telemetry will be performed during all rituximab infusions, and infusions will be discontinued in the event of serious or life threatening cardiac arrhythmias, and may be adjusted or discontinued in response to any other clinically significant findings, at the discretion of the Investigator. In addition,

patients who develop clinically significant arrhythmias may also undergo additional cardiac monitoring, also at the discretion of the Investigator.

Hepatitis B virus (HBV) reactivation along with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies. The rituximab prescribing information recommends that persons at high risk of HBV infection be screened before initiation of treatment, and that carriers of Hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following rituximab therapy. Due to the combined risk of HBV reactivation with rituximab and methotrexate-induced hepatotoxicity, patients who are at risk of HBV reactivation or who are known carriers of Hepatitis B (i.e., Hepatitis B surface antigen is positive) will be excluded from the current study.

The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or postmarketing reports with rituximab, the majority of these in patients receiving rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant: JC virus (progressive multifocal leukoencephalopathy [PML]), cytomegalovirus (CMV), herpes simplex virus, Parvovirus B19, varicella zoster virus, West Nile virus, and Hepatitis C. JC virus (PML) is a very rare complication of rituximab and usually occurs only in conjunction with the use of other immunosuppressants over an extended period of time; the disease usually leads to life-threatening disability and death over weeks to months. In some cases, viral infections occurred up to 1 year following discontinuation of rituximab and resulted in death.

4.4.2.3 Risks Associated With Methotrexate

A full description of methotrexate is in the local prescribing information (refer to Appendix 14.3). Investigators should familiarize themselves with any relevant premedication requirements, contraindications, warnings, precautions for use, and the AE profile provided therein. A summary of boxed warnings and contraindications relevant to this patient population is provided directly below.

Methotrexate should be administered only under the supervision of a physician experienced with antimetabolite treatments.

Deaths have been reported with the use of methotrexate in the treatment of malignancy, psoriasis, and rheumatoid arthritis. Patients should be closely monitored for bone marrow, liver, lung, and kidney toxicities.

Delayed drug clearance has been identified as one of the major factors for methotrexate toxicity. Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural

effusions. Such patients require especially careful monitoring for toxicity and require dose reduction or, in some cases, discontinuation of methotrexate administration.

Unexpectedly severe, and sometimes fatal, bone marrow suppression, aplastic anemia, and GI toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). With lower doses, NSAIDs and salicylates have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity. Therefore, concomitant administration of NSAIDs is strongly discouraged for patients receiving Regimen B in the current study.

Methotrexate should be used with extreme caution in the presence of active infection. Oral antibiotics, such as tetracycline, chloramphenicol, and non-absorbable broad spectrum antibiotics may decrease intestinal absorption of methotrexate or interfere with enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and GI toxicity have been observed with high- and low-dose methotrexate; use of methotrexate with penicillins should be carefully monitored. Sulfonamides also may decrease renal clearance of methotrexate and increase the risk of hematologic toxicity. Therefore, penicillins and sulfonamides should be used with extreme caution for patients receiving Regimen B in the current study.

Methotrexate causes hepatotoxicity, fibrosis, and cirrhosis, but generally only after prolonged use. Acute liver enzyme elevations are common; these are usually transient and asymptomatic, and do not appear predictive of later hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported. In rheumatoid arthritis patients persistent abnormalities in liver function tests may precede the appearance of fibrosis or cirrhosis, but in psoriasis patients these lesions are not necessarily preceded by symptoms or abnormal liver function tests. Methotrexate will be administered for a short duration in the current study; however, the possibility of liver lesions cannot be ruled out, and it is unknown whether such lesions, if they were to occur, would be preceded by clinical symptoms or abnormal liver function tests in Pompe patients.

Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. The prescribing information for methotrexate recommends interruption of treatment and careful investigation in the event of pulmonary symptoms, especially nonproductive dry cough. In patients with Pompe disease, monitoring for pulmonary toxicity may be complicated by pre-existing respiratory ailments due to disease progression. Therefore, it is suggested that patients

have a chest X-ray obtained prior to beginning their methotrexate dosing so that it may be used at a later time for comparison should respiratory complications arise during the study. In such patients, careful attention should be given to any worsening of symptoms and these should be thoroughly investigated prior to resuming the ITI regimen.

Diarrhea and ulcerative stomatitis require interruption of treatment; otherwise, intestinal perforation may lead to hemorrhagic enteritis and death.

Malignant lymphoma may occur with low-dose treatment and may regress when treatment is discontinued.

Severe, occasionally fatal skin reactions may occur within days after single or multiple doses. Recovery has been reported with discontinuation of therapy.

Potentially fatal opportunistic infections, especially *P. jiroveci* pneumonia, may occur with methotrexate therapy.

Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks.

Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate: during and for a minimum of 3 months after therapy for male patients, and during and for at least 1 ovulatory cycle after therapy for female patients. Because of the potential for serious adverse reactions from methotrexate in breast-fed infants, it is contraindicated in nursing mothers.

Limited experience in the treatment of polyarticular-course JRA shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses >20 mg/m^2/week in adults. Although there is experience with doses up to 30 mg/m^2/week in children, there are too few published data to assess how doses over 20 mg/m^2/week might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m^2/week may have better absorption and fewer GI side effects if methotrexate is administered either intramuscularly or SC.

4.4.2.4 Risks Associated With Intravenous Immunoglobulin

A full description of IVIG is in the local prescribing information (refer to Appendix 14.4). Investigators should familiarize themselves with any relevant pre-medication requirements, contraindications, warnings, precautions for use, and the AE profile provided therein. A

summary of warnings and contraindications relevant to this patient population is provided directly below.

The most significant risks associated with IVIG therapy are acute renal dysfunction, renal failure, osmotic nephrosis, and death. The IVIG local prescribing information contains a black box warning about risk of renal events. Patients in this study who are pre-disposed to renal disease are particularly susceptible to these events. The risk is increased in IVIG products containing sucrose. Per the local prescribing information, other risks associated with IVIG treatment include hemolysis, transfusion-related acute lung injury, thrombotic events, and aseptic meningitis syndrome.

5. STUDY OBJECTIVES

The objectives of this study are as follows:

1. To evaluate the efficacy of ITI regimens, as assessed by anti-rhGAA antibody titers, and antibodies that inhibit the enzymatic activity and/or uptake of Myozyme;
2. To evaluate Pompe disease activity in patients receiving these regimens, as measured by overall survival, respiratory function, left ventricular mass index (LVMI), motor function, and disability index; and
3. To evaluate the safety of these regimens, as assessed by the incidence of AEs, SAEs, and clinical laboratory abnormalities.

6. INVESTIGATIONAL PLAN

6.1 Study Design

This is an exploratory, open-label study of patients of any age with Pompe disease to evaluate the efficacy, safety, and clinical benefit of 2 ITI regimens in combination with Myozyme in patients receiving Myozyme treatment. The patient and/or the patient's legal guardian(s) must provide written informed consent prior to any protocol-related procedure being performed. Eligible patients who are currently receiving Myozyme therapy will be enrolled into the study, and will be followed for a minimum of 18 months on-study (a 6-month ITI treatment module and a 12-month follow-up module on Myozyme alone). Eligible CRIM-negative patients will be followed for a minimum of 18 months on treatment or, if a patient is <6 months of age at the time of enrollment, until the patient is 2 years of age.

Two ITI regimens will be evaluated in this protocol (see schematic in Figure 6-1):

- Regimen A: Patients will be assigned to Regimen A if they exhibit clinical decline since starting Myozyme therapy and have inhibitory antibodies and/or a sustained high anti-rhGAA antibody titer (defined as at least 2 titers ≥25,600 obtained at least 1 month apart), regardless of their CRIM status. Regimen A consists of a 6-month regimen of monthly cyclophosphamide. All cyclophosphamide infusions to patients with cardiomegaly or hypertrophic cardiomyopathy will be administered in a hospital and patients will be observed for a minimum of 24 hours post-infusion.
- Regimen B: Only CRIM-negative patients are eligible to enroll in Regimen B. CRIM-negative patients will be assigned to Regimen B if they either (1) exhibit clinical decline since starting Myozyme therapy and do not have inhibitory antibodies or a sustained high anti-rhGAA antibody titer (defined as at least 2 titers ≥25,600 obtained at least 1 month apart), or (2) do not exhibit clinical decline since starting Myozyme therapy, regardless of their anti-rhGAA or inhibitory antibody status. Regimen B consists of a 4-week cycle of weekly rituximab in combination with a 6-month regimen of biweekly methotrexate. An optional, additional cycle of rituximab (up to 4 additional doses) may be administered within the first 6 months of the study, as described in Section 8.1.

Patients on both regimens will receive IV infusions of Myozyme (20 mg/kg) qow for a minimum of 18 months or, if the patient is <6 months of age at the time of enrollment, until the patient is 2 years of age.

Any adjustments to a patient's ITI regimen (e.g., a decrease in dose) may be made in consultation with Genzyme and the ITIRB, if medically indicated, in an effort to allow the

patient to safely continue in the study while maintaining the potential clinical benefit of the regimen (see Section 7.4).

Clinical decline for patients regardless of CRIM status will be defined as decline in at least 1 of the following parameters as compared to the condition of the patient prior to beginning Myozyme treatment:

Cardiac

Persistence of a Left Ventricular Mass (LVM) Z-score ≥6 after a minimum of 6 months of treatment with Myozyme; OR

Respiratory

New development of respiratory failure requiring the use of ventilator assistance (invasive or non-invasive) after a minimum of 6 months of treatment with Myozyme. Ventilator assistance must have been required for at least 4 weeks prior to study enrollment; OR

Motor Skills

For patients ≤2 years of age at study entry, failure to acquire at least 2 new gross motor milestones or loss of at least 2 previously acquired gross motor milestones (or a combination thereof) after a minimum of 6 months of treatment with Myozyme, e.g.:

1. Turning head side to side (supine);
2. Grasping small objects with hands;
3. Transferring objects from hand to hand;
4. Holding head upright with body supported;
5. Rolling (supine to prone or prone to supine);
6. Sitting (supported or unsupported);
7. Walking (with support, i.e., cruising, or independently);
8. Walking up stairs (with assistance or independently); OR

Worsening of proximal upper extremity muscle weakness as determined by the Investigator through loss of functional use of the upper extremities after a minimum of 6 months of treatment with Myozyme; OR

Progression to use of an assistive device for ambulation due to worsening of proximal lower extremity muscle weakness after a minimum of 6 months of treatment with Myozyme.

Efficacy will be assessed by anti-rhGAA antibody titers; the evaluation of inhibitory antibody formation (activity and uptake); respiratory function as assessed by (a) the proportion of patients

who were alive and ventilator-free over the course of treatment, time to overall invasive ventilator-dependence, and ventilator-free survival time for patients who were ventilator-free at the onset of the study, and (b) the overall duration of ventilator support and the number of hours of ventilator use in the 24 hours preceding each infusion visit for patients who required ventilator use at the onset of the study; LVMI as assessed by echocardiogram (ECHO); and motor function and development as assessed by Gross Motor Function Measure-66 (GMFM-66), the Alberta Infantile Motor Scale (AIMS), and the Pompe Pediatric Evaluation of Disability Inventory (PEDI).

Patient safety will be monitored continuously throughout the study and evaluated in terms of AEs graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI/CTCAE), Version 3.0 (dated 09 August 2006); vital sign parameters; physical examination findings; electrocardiogram (ECG) parameters; routine laboratory measurements (chemistry, hematology, urinalysis); lymphocyte subpopulations; an immunoglobulin panel; and pregnancy testing. Specific attention will be given to any signs of infection or toxicity, including possible renal, hepatic, or pulmonary toxicity, or bone marrow suppression. Additional immunology measurements will include anti-rhGAA IgE, serum tryptase, complement activation, and skin testing, when clinically indicated following moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or recurrent mild (Grade 1) IARs to Myozyme that are suggestive of hypersensitivity; and circulating immune complex detection when clinically indicated by symptoms suggestive of immune complex disease.

Research immunophenotyping and functional T cell assays will also be performed as exploratory measures. Concomitant and pre-infusion medications and therapies will be monitored continuously throughout the study.

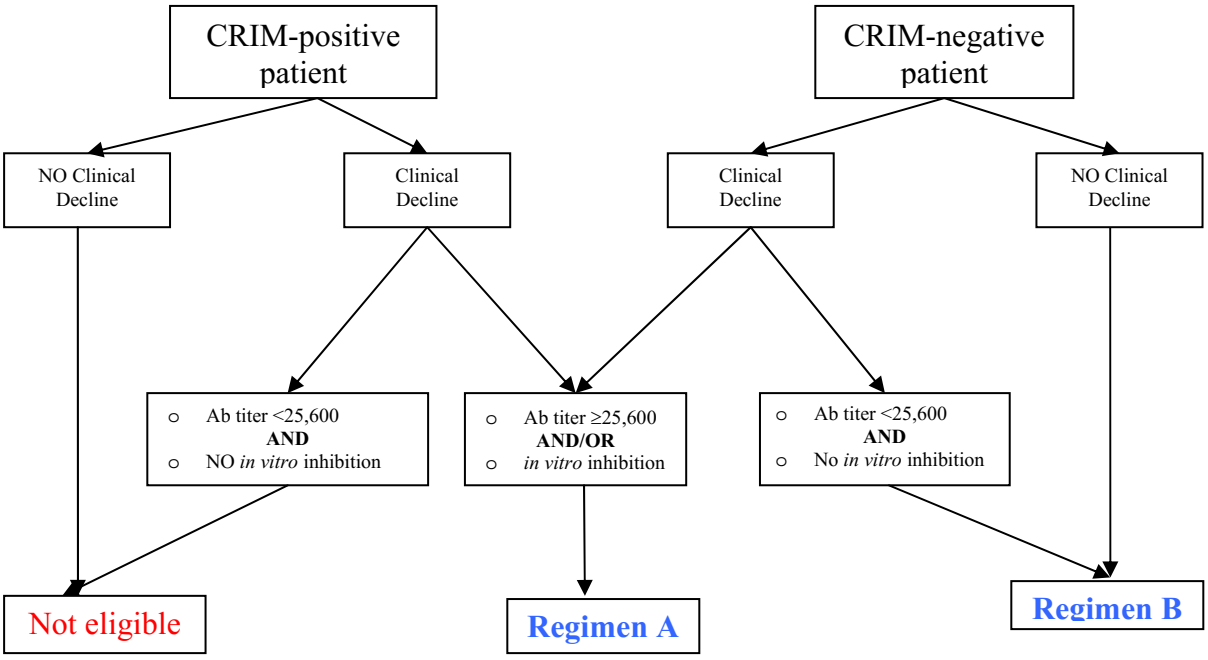
An ITIRB will evaluate the safety and efficacy of each of the ITI regimens after each patient completes 1 month of treatment on a given regimen, after each patient completes 6 months of treatment on a given regimen, and, if applicable, after the patient completes an optional, additional cycle of rituximab (if applicable), as well on an expedited *ad hoc* basis, as outlined in the ITIRB Charter (which is maintained separately from the protocol). The ITIRB will also provide recommendations about the risk/benefit profile of the ITI regimens; refer to Section 12.3 for further details.

An independent Allergic Reaction Review Board (ARRB) will be consulted on an *ad hoc* basis, as outlined in the ARRB Charter (which is also maintained separately from the protocol); refer to Section 12.4 for further details.

For consistency, a central cardiologist will review all ECGs and ECHOs.

Following study completion, patients may receive commercial Myozyme treatment as prescribed by their treating physician. To facilitate long-term data collection, patients will be encouraged to enroll in the Pompe Disease Registry after study completion.

Figure 6-1 Schematic of Patient Enrollment



7. PATIENT POPULATION AND SELECTION

It is planned that a total of 9 patients will initially be enrolled in the study. Patients will be assigned to either Regimen A or Regimen B based on their qualifications for a given regimen. Regimens will enroll as patients present until a total of 9 patients are treated. An attempt will be made to enroll a similar number of CRIM-positive and CRIM-negative patients on Regimen A, provided that sufficient number of qualified CRIM-negative patients can be identified within a reasonable study recruitment period. Enrollment will proceed in a sequential manner within each treatment regimen such that ITIRB review of data from the first patient within a regimen (for the first month of treatment) is completed prior to enrollment of any further patients on that regimen. If the regimen appears to have an acceptable risk/benefit profile after the first 3 patients in a given regimen have completed 1 month of treatment, additional patients may be enrolled as they present, or as necessary, to further evaluate the ITI regimen. Study patients will be enrolled at up to 9 centers.

7.1 Inclusion Criteria

Patients must meet the following criteria to be enrolled in this study:

1. The patient (and/or the patient's legal guardian[s] if the patient is <18 years of age) must provide written informed consent prior to any study-related procedures being performed;
2. The patient must have a clinical diagnosis of Pompe disease as defined by documented GAA deficiency (deficient endogenous GAA activity) in skin fibroblasts, muscle, or blood, or presence of 2 GAA mutations. Consent will also be sought from the biological parent(s) for parental GAA mutational analysis, but is not a requirement for study eligibility;
3. The patient (and/or the patient's legal guardian[s] if the patient is <18 years of age) must have the ability to comply with the clinical protocol;
4. If the patient is CRIM-positive, he/she must have received Myozyme therapy (20 mg/kg qow) for at least 6 consecutive months immediately prior to enrollment in the study.
5. If the patient is CRIM-negative, he/she must have received at least 1 Myozyme infusion prior to enrollment in the study;
6. Regimen A only:
   - The patient exhibits clinical decline (as defined in Section 6.1);
   - The patient has persistent high anti-rhGAA antibody titers (defined as at least 2 titers ≥25,600 obtained at least 1 month apart) and/or has tested positive for antibodies that inhibit enzymatic activity and/or uptake of Myozyme.

7. Regimen B only:
    - The patient is CRIM-negative via Western blot analysis of skin fibroblasts; AND
    - The patient does NOT exhibit clinical decline (as defined in Section 6.1); OR
    - The patient is CRIM-negative via Western blot analysis of skin fibroblasts; AND
    - The patient exhibits clinical decline (as defined in Section 6.1); AND
    - The patient does NOT have persistent high anti-rhGAA antibody titers (defined as at least 2 titers ≥25,600 obtained at least 1 month apart) and has NOT tested positive for antibodies that inhibit enzymatic activity and/or uptake of Myozyme.

Note that historical CRIM testing results by Western blot analysis (performed prior to enrollment) are acceptable, provided that written documentation of the laboratory results is available at the enrolling site.

7.2 Exclusion Criteria

Patients will be excluded from this study if they do not meet the specific inclusion criteria, or if they meet the following exclusion criteria:

1. The patient has any medical condition that, in the opinion of the Investigator, could interfere with the study regimens (i.e., Myozyme, cyclophosphamide, rituximab, IVIG, and/or methotrexate) or assessments; such conditions may include, but are not limited to, active human immunodeficiency virus infection, cancer, or tuberculosis;
2. The patient is at risk of reactivation or is a carrier of Hepatitis B (e.g., Hepatitis B surface antigen is positive) or Hepatitis C (e.g., detectable Hepatitis C viral load by reverse transcriptase – polymerase chain reaction);
3. The patient is at risk of reactivation or has positive serology suggestive of active infection for CMV, Herpes simplex, JC virus (PML), Parvovirus, or Epstein Barr virus;
4. The patient is at risk of reactivation of tuberculosis or has regular contact (e.g., in the household) with individuals who are being actively treated for tuberculosis;
5. The patient has low serum albumin, relative to institutional age-appropriate range, that is uncorrected;
6. The patient has a major congenital abnormality;
7. The patient has used any investigational product (other than Myozyme in those regions where the product is not commercially available and is considered investigational) within 30 days prior to study enrollment;

8. The patient is pregnant or lactating;
9. The patient has had or is required to have any live vaccination within 1 month prior to enrollment.

At the discretion of the Investigator, clinical laboratory test results that are deemed to be due to transient illness may be repeated for the purpose of determining study eligibility.

7.3 Patient Withdrawal

7.3.1 Patient Withdrawal From the Study

Patient participation in this study is voluntary. The patient (and/or the patient's legal guardian(s) if the patient is <18 years of age) is free to withdraw consent and discontinue participation in the study at any time, and without prejudice to further treatment.

Any female patient who becomes pregnant will be discontinued from the study.

A patient's participation in the study may also be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a patient from the study:

- Parents/guardians are non-compliant and will not adhere to study responsibilities, including failure to appear at study visits;
- The patient was erroneously included in the study;
- The patient develops an exclusion criterion or concurrent disease;
- The patient suffers an intolerable AE;
- The patient receives other investigational products, interventions, or procedures during the study;
- The patient suffers severe toxicity or infection and supportive treatment and/or regimen adjustment are deemed to be inadequate to resolve the toxicity or infection, or are inconsistent with the patient's ability to safely complete the protocol (see Section 7.3.2 for guidelines);
- The study is terminated by the Sponsor.

For patients who discontinue early from the study, or if the study is prematurely terminated by the Sponsor, the Investigator or designee will contact the patient and/or the patient's legal guardian(s) within 4 to 7 days after withdrawal or termination to obtain information about the reason(s) for discontinuation and to assess for any AEs. The Investigator should collect information pertaining to new AEs and follow-up ongoing AEs. In addition, the Investigator should immediately contact Genzyme to discuss the reasons for the patient's discontinuation.

All patients should return to the clinic for the final clinical assessments (Week 75, Day 518 assessments listed in Table 9-3) within 14 days, unless otherwise specified. All AEs ongoing at the time of withdrawal or study termination require a 30-day follow up. The Investigator will provide a written report on the Completion/Discontinuation section of the electronic case report form (eCRF), describing the reason for discontinuation. The Investigator will attempt to collect all withdrawal assessments if a patient discontinues from the study. The Investigator will be asked to follow all SAEs that were ongoing at the time of withdrawal or termination until resolution (and information reported to Genzyme Global Patient Safety and Risk Management [GPS-RM]), until the Investigator deems follow-up is no longer medically necessary, or until the patient is lost to follow-up.

In addition, if a patient in Regimen B discontinues the study for any reason during the ITI treatment module, the Investigator will continue to follow-up with the patient for a period of at least 45 days after the last dose of rituximab is administered (at a medically appropriate frequency to be determined by the Investigator) to monitor for any new AEs that may be suggestive of immunosuppressant-induced toxicity and/or are secondary to immunosuppression.

Because there have been documented incidents of delayed onset of AEs related to rituximab administration (Ram, 2009, *Leukemia Lymphoma*), it is recommended that physicians report any AEs suggestive of immunosuppressant-induced toxicity to the product manufacturer in addition to Genzyme as a spontaneous report. For patients who have withdrawn consent or who have otherwise completed the clinical study, these data will not be included in the clinical study database, but will be maintained in the GPS-RM surveillance database.

In the event that a patient dies, permission will be sought (through a separate informed consent form) from the next of kin or the patient's legal guardian(s) for a research autopsy or post-mortem research biopsy. Samples collected from these procedures will be used for research purposes only and data will not be provided to the Investigator or be included in any study analyses.

7.3.2 Patient Withdrawal From the Immune Tolerance Induction Regimen

Patients will be carefully monitored for any signs of infection or toxicity during the study. If any of the criteria below are met during administration of the ITI regimen, the regimen will be temporarily discontinued to permit further evaluation of the patient by the Investigator in consultation with Genzyme (and the ITIRB, as appropriate). Additionally, the regimen may also be temporarily or permanently discontinued in response to other clinically significant findings, at the discretion of the Investigator.

- The patient exhibits unacceptable renal toxicity, as defined by a >2x increase in serum creatinine from the baseline value with a resultant value that is above the normal range.

If a >2x increase from baseline is observed and the resultant value is still within the normal range, the patient may continue on the immunosuppressive regimen at the discretion of the Investigator;

- The patient exhibits unacceptable liver toxicity, as defined by a >3x increase in AST or ALT from the respective baseline values and/or an increase in direct, indirect or total bilirubin of >3x the upper limit of normal;
- The patient exhibits significant worsening of pulmonary symptoms;
- The patient develops an infection that is resistant to treatment;
- The patient exhibits signs of significant bone marrow suppression, as defined by a platelet count of <50,000/mm^3 or a neutrophil count <500/mm^3;
- The patient has significant red cells in the urine and/or symptoms suggestive of severe hemorrhagic cystitis;
- Any SAE occurring during the study that is ≥Grade 4 (according to NCI/CTCAE, Version 3.0), and assessed as related to any of the study medications or procedures.

For the purpose of this study, if any of the above criteria are met or if the regimen is discontinued by the Investigator due to other clinically significant findings, the results will be considered indicative of a definite or possible stopping rule. The Investigator is responsible for notifying the relevant Institutional Review Board (IRB) and Genzyme GPS-RM via phone, fax, or e-mail when a stopping rule has been met or when a possible stopping rule is being evaluated. Any findings determined to be a stopping rule will be reported to the regulatory authorities by the Sponsor when appropriate. See Section 9.7 for the specific stopping rules for this study.

Pending the outcome of further evaluation of the patient (and, as appropriate, an *ad hoc* review of safety data conducted by the ITIRB as outlined in Section 12.3), the regimen may be permanently discontinued, continued at the same dose, or continued at an adjusted dose in select or all patients.

7.3.3 Patient Replacement

Given the small size of the AGLU03707 study, if a patient prematurely discontinues the study for any reason, additional patients may be enrolled to ensure that a sufficient number of patients complete the study to evaluate the efficacy and safety of the ITI regimens.

7.4 Adjustments to Dose or Dosing Schedule

Pretreatment, rate reduction, or postponement of dosing (e.g., due to transient patient illness) are permitted, at the discretion of the Investigator, to prevent and/or manage adverse drug reactions.

In the event that a patient is unable to tolerate the per-protocol regimen despite the use of pretreatments, rate reduction, and/or supportive measures (see Section 8.3), an adjustment in the dose of Myozyme, cyclophosphamide, rituximab, methotrexate, and/or IVIG, may be made, if medically indicated, to enable a patient to safely continue in the study while maintaining the potential clinical benefit of the regimen. All such dose adjustments must be discussed with and approved by the Genzyme GPS-RM Safety Officer or designee, prior to implementation. At the discretion of Genzyme, such dose adjustments may also be reviewed by the ITIRB prior to implementation.

A patient on Regimen B who completes the initial cycle of rituximab treatment may be considered for an optional, additional cycle of rituximab (up to 4 additional doses) within the first 6 months of the study, as described in Section 8.1, if it is felt that he/she would benefit from continuing the regimen, either because he/she responded favorably to the initial treatment cycle or because he/she failed to exhibit a satisfactory response to the initial treatment cycle in terms of clinical response and/or antibody titer. This additional cycle must be completed within the first 6 months of the study.

7.5 Study or Site Termination

If the Study Director, Medical Monitor, GPS-RM Safety Officer, Investigator, Regulatory Authorities, or IRB discover conditions during the study that indicate that the study or site should be terminated, this action may be taken after appropriate consultation between the Investigator and Genzyme's Medical Monitor. Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study;
- The decision on the part of Genzyme to suspend or discontinue testing, evaluation, or development of the study drug;
- Failure of the Investigator to comply with pertinent local and national regulations;
- Submission of knowingly false information from the research facility to Genzyme, IRB or any national regulatory officials;
- Non-adherence to protocol requirements.

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines.

8. TREATMENTS

8.1 Treatments Administered

The treatments to be administered in this study are summarized below by regimen.

Patients on Regimen A

- Myozyme: 20 mg/kg IV qow for a minimum of 18 months or, if the patient is <6 months of age at the time of enrollment, until the patient is 2 years of age.
- Cyclophosphamide: 250 mg/m^2 IV every 4 weeks after Myozyme infusion for 6 months.

The first 5 weeks of treatment for Regimen A are shown in Table 8-1 below.

Table 8-1 Treatment Regimen A

	W1[a]	W2[a]	W3[a]	W4[a]	W5[a]
	D0	D7	D14	D21	D28
Myozyme	X		X		X
Cyclophosphamide[b]	X				X

[a] Weeks 2 to 5 will be repeated through Week 24 for Myozyme and cyclophosphamide AND from Week 25 to Week 75 for Myozyme.
[b] Refer to Table 9-1 for further information regarding the administration of cyclophosphamide.
Note: It is recommended that the Investigator monitor a patient's immunoglobulin levels and consider IVIG administration at a dose of 400 mg/kg, regardless of age, if indicated per the individual Investigator's clinical discretion.
Key: W=Week; D=Day

Patients on Regimen B

- Myozyme: 20 mg/kg IV qow for a minimum of 18 months or, if the patient is <6 months of age at the time of enrollment, until the patient is 2 years of age.
- Rituximab: 375 mg/m^2 (or 12.5 mg/kg in those patients with a BSA ≤0.5 m^2) IV weekly for 4 weeks, beginning the day after the first Myozyme infusion. An optional, additional 4-week cycle of rituximab (up to 4 additional doses) may be administered within the first 6 months of the study. The administration of an additional cycle of rituximab must be discussed with and approved by the Genzyme GPS-RM Safety Officer, or designee, prior to implementation and may, at the discretion of Genzyme, also be reviewed with the ITIRB prior to implementation. This additional cycle must be completed within the first 6 months of the study. If the additional cycle is approved, these data will be included in the 6-month periodic ITIRB review. The total number of rituximab doses will not exceed 8 doses.

- Methotrexate: 15 mg/m^2 SC qow on the day after Myozyme infusion for 6 months (12 doses). Folinic acid may be given at the discretion of the Investigator beginning 24 hours after the dose of methotrexate.

The first 6 weeks of treatment for Regimen B are shown in Table 8-2 below.

Table 8-2 Treatment Regimen B

	W1		W2	W3		W4	W5[a]		W6[a]
	D0	D1	D8	D14	D15	D22	D28	D29	D35
Myozyme	X			X			X		
Rituximab[b,c]		X	X		X	X			
Methotrexate[c]		X			X			X	

[a] Weeks 5 and 6 will be repeated through Week 24 for Myozyme and methotrexate AND from Week 25 to Week 75 for Myozyme.
[b] An optional, additional 4-week cycle of rituximab (up to 4 additional doses) may be administered as described above. This additional cycle must be completed within the first 6 months of the study.
[c] Refer to Table 9-2 for additional information pertaining to administration of rituximab and methotrexate.
Note: It is recommended that the Investigator monitor a patient's immunoglobulin levels and consider IVIG administration at a dose of 400 mg/kg, regardless of age, if indicated per the individual Investigator's clinical discretion.
Key: W=Week; D=Day

For both treatment regimens, the Investigator or appropriate designee should evaluate the patient prior to the administration of any study medications (Myozyme, cyclophosphamide, rituximab, and/or methotrexate). This should include a brief physical examination and review of the most recent laboratory tests and vital signs to specifically ensure that the patient is clinically stable and can tolerate administration of these agents. Dosing should be postponed if the patient is acutely ill on a scheduled dosing day.

Adjustments to the planned doses and/or dosing schedules for the study treatments are discussed in Section 7.4.

8.1.1 Myozyme

Patients will receive Myozyme (20 mg/kg qow) as an IV infusion, according to the Myozyme Investigator's Brochure. The total amount of Myozyme administered may be adjusted as needed to account for changes in body weight.

Clinical management guidelines for Myozyme can be found in the local prescribing information. Myozyme should be infused in a dedicated IV line. Infusions should be administered in a step-wise manner. Vital signs should be monitored as described in Section 9.4.4. It is recommended that the infusion should begin at an initial rate of approximately 1 mg/kg/hour and may be incrementally augmented, if there are no signs of IARs, until a maximum rate of approximately 7 mg/kg/hour is reached, as follows:

- Step 1: approximately 1 mg/kg/hour administered over a minimum of 30 minutes
  – If no signs of IARs go to next step;
- Step 2: approximately 3 mg/kg/hour administered over a minimum of 30 minutes
  – If no signs of IARs go to next step;
- Step 3: approximately 5 mg/kg/hour administered over a minimum of 30 minutes
  – If no signs of IARs go to next step;
- Step 4: approximately 7 mg/kg/hour administered for the remainder of the infusion.

IARs are more likely to occur at higher infusion rates. For this reason, the infusion rate may be slowed and/or temporarily stopped in the event of an IAR.

The length of infusion is approximately 3.5 to 4 hours for a dose of 20 mg/kg. Specific details pertaining to the infusion volumes and rates can be found in the Investigational Product Handling Manual.

Patients should continue to be observed for occurrence of AEs for 2 hours after each infusion.

Authorized medical personnel will be responsible for the administration of investigative agents throughout the study and should document in the medical record the rationale for making any changes to the administration steps outlined in this section.

8.1.2 Cyclophosphamide

Cyclophosphamide 250 mg/m^2 will be given IV according to the local prescribing information (refer to Appendix 14.1).

Patients in Regimen A who have cardiomegaly or hypertrophic cardiomyopathy will be admitted to the hospital for all cyclophosphamide infusions, and will remain in the hospital for observation for a minimum of 24 hours after completion of the infusion.

A complete blood count (CBC) with differential, Chemistry, CK and CK-MB, and urinalysis should be performed prior to each cyclophosphamide infusion, and all laboratory results should be reviewed by the Investigator prior to the start of the infusion. Results of the most recent immunoglobulin panel should also be reviewed prior to the infusion.

Telemetry should be performed during each cyclophosphamide infusion to patients with cardiomegaly or hypertrophic cardiomyopathy from at least 10 minutes prior to the start of the infusion until at least 2 hours post-infusion. Infusions will be discontinued in the event of serious or life-threatening cardiac arrhythmias, and may be adjusted or discontinued in response to any other clinically significant findings, at the discretion of the Investigator. At the discretion of the Investigator, patients who develop clinically significant arrhythmias may also undergo additional cardiac monitoring.

Prior to dosing, Investigators should familiarize themselves with any relevant premedication requirements, contraindications, warnings, precautions for use, and the AE profile, as provided in the local prescribing information (refer to Appendix 14.1).

8.1.3 Rituximab

Rituximab 375 mg/m^2 (or 12.5 mg/kg in those patients with a BSA ≤0.5 m^2) will be given IV according to the local prescribing information (refer to Appendix 14.2).

Patients in Regimen B will be admitted to the hospital for all rituximab infusions, and will remain in the hospital for observation for a minimum of 24 hours after completion of the infusion.

The Investigator should consider pretreatment with antihistamines and acetaminophen as suggested in the rituximab local prescribing information (refer to Appendix 14.2).

A CBC with differential, Chemistry, CK and CK-MB, and urinalysis will be performed prior to each rituximab infusion, and all laboratory results will be reviewed by the Investigator prior to the start of the infusion. Results of the most recent immunoglobulin panel will also be reviewed prior to the infusion; an *ad hoc* immunoglobulin panel may be ordered at the discretion of the Investigator (depending upon when the most recent results were reported).

Telemetry should be performed during each rituximab infusion from at least 10 minutes prior to the start of the infusion until at least 2 hours post-infusion. Infusions will be discontinued in the event of serious or life-threatening cardiac arrhythmias, and may be adjusted or discontinued in response to any other clinically significant findings, at the discretion of the Investigator. At the discretion of the Investigator, patients who develop clinically significant arrhythmias may also undergo additional cardiac monitoring.

Prior to dosing, Investigators should familiarize themselves with any relevant premedication requirements, contraindications, warnings, precautions for use, and the AE profile for rituximab, as provided in the local prescribing information (refer to Appendix 14.2).

8.1.4 Methotrexate

Methotrexate 15 mg/m^2 will be given SC according to the local prescribing information (refer to Appendix 14.3).

A CBC with differential, Chemistry, CK and CK-MB, and urinalysis will be performed prior to each SC dose of methotrexate, and all laboratory results will be reviewed by the Investigator prior to the dose of methotrexate being administered. Results of the most recent immunoglobulin panel should also be reviewed prior to dosing; an *ad hoc* immunoglobulin panel may be ordered at the discretion of the Investigator (depending upon when the most recent results were reported).

Folinic acid supplementation may be given at the discretion of the Investigator beginning 24 hours after the dose of methotrexate.

Prior to dosing, Investigators should familiarize themselves with any relevant premedication requirements, contraindications, warnings, precautions for use, and the AE profile, as provided in the local prescribing information (refer to Appendix 14.3).

8.1.5 Intravenous Immunoglobulin

It is recommended that the Investigator monitor a patient's immunoglobulin levels and consider IVIG administration at a dose of 400 mg/kg, regardless of age, if indicated per the individual Investigator's clinical discretion.

Prior to dosing, Investigators should familiarize themselves with any relevant premedication requirements, contraindications, warnings, precautions for use, and the AE profile for IVIG, as provided in the local prescribing information (refer to Appendix 14.4).

8.2 Investigational Products

Myozyme will be supplied as a lyophilized product in single-use 20 mL vials containing approximately 50 mg/vial of Myozyme. This product must be stored in a secure location with limited access, under adequate refrigerated temperature conditions (2 degrees Celsius [°C] to 8°C). Re-constituted Myozyme should be protected from light.

Commercial methotrexate sodium for injection (a formulation not containing benzyl alcohol) will be obtained by Genzyme and supplied in commercial packaging with appropriate supplemental labeling. Methotrexate should be stored at controlled room temperature (20°C to 25°C) and protected from light.

A liquid concentrate of rituximab intended for IV administration via a dedicated line will be obtained by Genzyme and supplied in commercial packaging with appropriate supplemental labeling. Rituximab must be stored under controlled, refrigerated conditions (2°C to 8°C) and protected from light.

Lyophylized cyclophosphamide for IV injection or infusion will be obtained by Genzyme and supplied in commercial packaging with appropriate supplemental labeling. Prior to reconstitution, cyclophosphamide must be stored at or below 25°C (the upper limit of controlled room temperature). Reconstituted cyclophosphamide is chemically and physically stable for up to 24 hours at controlled room temperature and up to 6 days under refrigerated conditions; it does not contain any antimicrobial preservatives and thus care must be taken to assure the sterility of prepared solutions.

IVIG (human) is a sterile, highly purified, and concentrated source of IgG antibodies, prepared from large pools of human plasma. It is available as a 10%, ready-to-use, liquid formulation in

various brands. It will be provided to participating sites for study patients, as defined in Section 8.1, in commercial packaging with supplemental labeling. IVIG should be stored according to the manufacturer's instructions.

IVIG should be administered via a dedicated line, in a step-wise fashion, at the minimum rate of infusion, as practical. Refer to the product-specific local prescribing information for infusion rates. Investigators should be familiar with IVIG therapy and the risks associated with it. Administration should be conducted in accordance with the product's local prescribing information and the institutional guidelines of the participating site.

All investigational medications must be stored in a secure area with limited access.

Additional details can be found in the Investigational Product Handling Manual. For a full description of rituximab, methotrexate, cyclophosphamide, and IVIG storage instructions, refer to the respective local prescribing information (refer to Appendices 14.1 through 14.4).

8.2.1 Receipt of Investigational Product

If the shipment was received as stated, the Investigator or designee must place a check mark in the Received/Verified box, and then sign and date the Proof of Receipt (POR) form. The form must then be faxed to Genzyme (number listed on POR form) within 48 hours of receipt. If there are any discrepancies with the shipment, Genzyme should be contacted immediately (contact information is listed on the POR form). A copy of this form must be retained in the site files.

The clinical supplies are to be prescribed only by the Investigator(s) named on the US Food and Drug Administration Form 1572. Under no circumstance will the Investigator or Sub-Investigator allow the investigational products to be used other than as directed by the protocol.

8.2.1.1 Packaging and Labeling

Genzyme's Clinical Pharmacy Research Services (CPRS) will manage packaging and labeling of the Investigational product.

Vials of Myozyme will be packaged in appropriately sized kits. Each vial and kit will be labeled with a single-panel label. Label text will minimally include the contents of the vial, lot number, storage conditions, Genzyme's name and address, and the statement "Caution: New Drug - Limited by Federal (or US) law to investigational use." Each kit label will have a space for the patient's identification number, date of birth, and initials to be handwritten by the clinical site upon receipt of product.

Vials of cyclophosphamide, rituximab, methotrexate, and IVIG will be supplied in commercial packaging with appropriate supplemental labeling provided by Genzyme.

8.2.1.2 Treatment Preparation

Infusions must be prepared by a qualified, authorized pharmacist (or designee) using aseptic technique. The pharmacist or designee will determine the dose and quantity of vials required based on the patient's weight (Myozyme, IVIG) or BSA (rituximab, methotrexate, cyclophosphamide), as determined monthly. BSA area should be calculated using the Haycock formula (Haycock, 1978, *J Pediatr*): BSA (m^2) = $Height^{(0.3964)}$ * $Weight^{(0.5378)}$ * 0.024265, where height is in cm and weight is in kg.

Each vial of Myozyme is reconstituted with 10.3 mL of sterile water for injection to yield a 5 mg/mL solution. The volume required for the dose must be withdrawn from each vial slowly to avoid foaming. The reconstituted solution should be further diluted into a fixed total volume of 0.9% sodium chloride for injection, dependant on patient weight (kg) and dose (mg/kg). The concentration of the final solution must be between 0.5 to 4 mg/mL. Further information on the preparation and administration of Myozyme is provided in the Investigational Product Handling Manual.

For a full description of cyclophosphamide, rituximab, methotrexate, and IVIG preparation and administration instructions, refer to the respective local prescribing information (refer to Appendices 14.1 through 14.4).

8.3 Supportive Measures

Necessary supportive measures for optimal medical care are to be given throughout the study as medically indicated, and according to the site's guidelines and the judgment of the Investigator. Some general guidelines for the management of toxicity and infection are provided in the sections below. Investigators should familiarize themselves with all warnings, contraindications, and precautions for use for cyclophosphamide, rituximab, methotrexate, and IVIG as provided in the respective local prescribing information.

All concomitant medications and relevant supportive therapy must be recorded in the appropriate eCRF.

8.3.1 Gastrointestinal Toxicity

Gastrointestinal toxicity, including nausea, vomiting, and diarrhea, have been reported with methotrexate treatment. Administration of methotrexate should be postponed for patients experiencing vomiting or diarrhea until the patients have recovered and are adequately re-hydrated (see Section 8.3.5).

8.3.2 Nephrotoxicity

Methotrexate-induced nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in renal tubules. Close attention to renal function including adequate

hydration (see Section 8.3.5) and monitoring of serum creatinine levels is essential. At the discretion of the Investigator, a prophylactic regimen of allopurinol may be administered (for urine alkalinization) to reduce the potential risk of renal toxicity. Concomitant administration of other nephrotoxic agents should be avoided wherever possible.

See also Section 7.3.2, Patient Withdrawal from the ITI Regimen.

8.3.3 Hepatotoxicity

Methotrexate causes hepatotoxicity, fibrosis, and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen, and are usually transient and asymptomatic, although not always predictive of subsequent hepatic disease. Liver enzymes should be closely monitored for any sustained increases in AST or ALT that exceed the transient elevations that may occur secondary to muscle cell damage in patients with Pompe disease. Concomitant administration of other hepatotoxic agents should be avoided wherever possible.

See also Section 7.3.2, Patient Withdrawal from the ITI Regimen.

8.3.4 Pulmonary Toxicity

Pulmonary symptoms (especially a dry non-productive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion, and can occur acutely and at any dose. Therefore, any further deterioration in a patient's pulmonary function following administration of methotrexate should be carefully investigated prior to resuming the ITI regimen, e.g., a chest X-ray may performed, if medically indicated.

See also Section 7.3.2, Patient Withdrawal from the ITI Regimen.

8.3.5 Hydration

It is recommended that the patient's fluid status be carefully monitored during administration of methotrexate to reduce the risk of potential renal and hepatic toxicity. Careful monitoring of fluid status is also important during administration of cyclophosphamide to reduce the risk of hemorrhagic cystitis. Patients should be well-hydrated prior to methotrexate or cyclophosphamide administration. However, because patients with Pompe disease are at risk for cardiopulmonary complications, a cardiologist should be consulted regarding patients' cardiac status to determine appropriate hydration and avoid volume overload.

8.3.6 Infection

Infection control is an integral part of the management of immunosuppressed patients, including children, adolescents, and adults. It is recommended that the Investigator follow the infection control guidelines detailed in the Red Book (*Red Book: Infection Control in Hospitalized Children and Physician Offices*, 2003). The patient and/or legal guardian(s) should be instructed in the techniques used to prevent the transmission of infections in the household.

Infection prophylaxis for *P. jiroveci* (formerly known as *P. carinii)* using Trimethoprim sulfa (Bactrim®) or alternate regimens at the age-appropriate recommended doses is advised for patients who are >6 years of age and have moderate (750 to1499 CD4 cell count) to severe (<750 CD4 cell count) immunosuppression, as per the current guidelines for prophylaxis against *P. jiroveci* in immunocompromised children (Centers for Disease Control and Prevention, 1995) and available online (http://www.cdc.gov/mmwr/preview/mmwrhtml/00037275.htm). Prophylaxis for other opportunistic bacterial, fungal, and/or viral infections may also be considered at the discretion of the Investigator and in accordance with current pediatric antimicrobial prophylaxis guidelines (*Red Book*: *Antimicrobial Prophylaxis,* 2003).

Patients should be monitored closely for any sign of infection, with consequent aggressive treatment and management, should this occur. In selecting an antibiotic to treat the infection, attention should be given to potential drug interactions among the investigative agents and certain antibiotics. For patients on Regimen B, sulfonamides and penicillins should be used with extreme caution due to the potential for these agents to reduce the renal clearance of methotrexate with a resultant increased risk of hematologic and/or GI toxicity. It is recommended that an infectious disease specialist be consulted whenever any antimicrobial agent is to be administered for the treatment of active infection in patients receiving Regimen B.

Vaccination with live virus is prohibited within 1 month prior to enrollment in this study and until a patient's B cell count returns to normal, or at least 3 months following completion of the ITI regimen, whichever is longer. While inactivated vaccines are permitted, the effectiveness of inactive virus given concomitantly with cyclophosphamide, rituximab, or methotrexate is questionable. However, patients undergoing ITI regimens may benefit from specific immunizations directed at preventing infections by organisms to which they are particularly susceptible; special consideration should be given to the administration of pneumococcal, influenza, and/or meningococcal vaccines, and any other recommendations for immunosuppressed patients, as outlined in the Red Book (*Red Book*: *Immunizations in Special Clinical Circumstances,* 2003).

Further information regarding infection prophylaxis and the treatment of active infection is provided in the SOM.

See also Section 7.3.2, Patient Withdrawal from the ITI Regimen.

8.3.7 Anaphylactic/Allergic Reactions

Serious and potentially life-threatening hypersensitivity reactions, including anaphylaxis, have been reported following administration of Myozyme, rituximab, and cyclophosphamide, which could be worse in patients with advanced Pompe disease who may already have compromised cardiac and respiratory function. Therefore, appropriate medical support measures, including

cardiopulmonary resuscitation equipment, should be readily available during administration of these agents. All cyclophosphamide infusions to patients with cardiomegaly or hypertrophic cardiomyopathy and all rituximab infusions will occur in a hospital setting, and patients will remain in the hospital for a minimum of 24 hours post-infusion.

Pretreatments may be administered prior to rituximab infusion as per guidelines in the local prescribing information. Investigators should also familiarize themselves with the prescribing information on the management of rituximab AEs.

Guidance on the management of Myozyme IARs, including recommended pretreatments, is provided in Appendix 1 of the current Myozyme Investigator's Brochure.

8.4 Concomitant Medication/Therapy

Other than those designated in the study regimen, no concomitant cytotoxic therapy or investigational therapy is allowed during the study.

Patients on both regimens may not receive any live vaccines within 1 month prior to enrollment and until B cell count returns to normal or at least 3 months following completion of the ITI regimen, whichever is longer. Use of alternative medications (e.g., herbal, botanical, etc) is strongly discouraged during the entire study period for all patients.

Caution should be used when administering general anesthesia for the placement of a central venous catheter or other surgical procedures in infantile-onset Pompe disease patients with cardiac hypertrophy (see Section 4.4.1.3). Caution should also be exercised in administering general anesthesia to patients receiving cyclophosphamide during the ITI Treatment Module for Regimen A (see Section 4.4.2.1).

For patients receiving Regimen B, concomitant administration of NSAIDs is strongly discouraged for the duration of the ITI Treatment Module, due to reports of unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and GI toxicity with concomitant administration of methotrexate (usually in high dosage) along with some NSAIDs. To the extent possible, use of nephrotoxic (e.g., vancomycin, amphotericin B, etc) and hepatotoxic (e.g., voriconazole, cyclosporine, etc) agents is also to be avoided for the duration of administration of the ITI regimen due to potential increased risk of nephrotoxicity and hepatotoxicity when administered in combination with methotrexate. Sulfonamides and penicillins should be used with extreme caution due to the potential for these agents to reduce the renal clearance of methotrexate with a resultant increased risk of hematologic and/or GI toxicity; it is recommended that an infectious disease specialist be consulted whenever any antimicrobial agent is to be administered for the treatment of active infection in patients receiving this regimen. Folinic acid supplementation may be given at the discretion of the Investigator.

8.5 Study Drug Misdosing or Overdosing

In the event that a patient is misdosed or overdosed, refer to the Myozyme Investigator's Brochure or the local prescribing information for the specific agents.

8.6 Dose Selection

Selection of the doses of Myozyme, cyclophosphamide, rituximab, and methotrexate was based on nonclinical and clinical experience with the agents, as outlined in Section 4.2 for Myozyme and Section 4.3.1 to Section 4.3.3 for the immunosuppressant agents.

8.7 Blinding and Randomization

This is an open-label study.

9. EFFICACY AND SAFETY VARIABLES

9.1 Efficacy and Safety Measurements Assessed and Study Schedule of Assessments

The study will be conducted as outlined in the following sections. Study assessments will be performed according to the Schedule of Assessments for the ITI treatment module (Months 1 through 6) and the follow-up module (Months 7 through 18). The Schedules of Assessments for the Regimen A ITI treatment module and Regimen B ITI treatment module are provided in Table 9-1 and Table 9-2, respectively. The Schedule of Assessments for the follow-up module, which is identical for both regimens, is provided in Table 9-3. The Schedule of Assessments for patients who enroll before 6 months of age and therefore must be on the study for longer than 18 months is provided in Appendix 14.6. Specific details of the study assessments are provided in Section 9.2 through Section 9.6, and in the SOM.

Guidance on the relative priority of each assessment is provided in the SOM, in the event that there is insufficient blood volume to complete all study laboratory assessments, or insufficient time to complete all assessments at a given study visit. During the ITI treatment module, a visit window of ± 7 days will be permitted for the Pompe PEDI, GMFM-66, and AIMS assessments; all remaining assessments should be conducted at the indicated visit in the Schedule of Assessments. A visit window of ± 2 weeks (14 days) will be permitted for all study assessments during the follow-up module; however, the visit window is ±1 week for Myozyme infusions. Eligible CRIM-negative patients will be followed for a minimum of 18 months on treatment or, if the patient is <6 months of age at the time of enrollment, until the patient is 2 years of age.

Table 9-1 Schedule of Assessments – Regimen A ITI Treatment Module (Months 1 Through 6)

	Month 1									Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4				W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 20	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
Informed Consent	X																												
Confirmation of Inclusion/Exclusion Criteria[1]	X																												
Demographics	X																												
Medical/Surgical/ Pompe Disease History[2]	X																												
Genetic Mutation Analysis[3]	X																												
Optional Parental GAA Mutation Analysis[3]	X																												
Pregnancy testing[4]	X		X							X				X				X				X				X			
Optional Porta-Catheter Placement	X																												
Physical Examination[5]	X	X	X		X	X		X		X		X		X		X		X		X		X		X		X		X	
Research Immunophenotyping		X			X	X		X										X								X			
Lymphocyte Subpopulation Counts		X			X	X		X										X								X			
Functional T cell Assay (ELISPOT)		X			X	X		X				X						X								X			
Immunoglobulin Panel[6]		X						X				X		X				X				X				X			

Table 9-1 Schedule of Assessments – Regimen A ITI Treatment Module (Months 1 Through 6) (continued)

	Month 1									Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4				W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 20	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
CBC with Differential[6]	X	X	X		X	X		X		X		X		X		X		X		X		X		X		X		X	
Chemistry, CK and CK-MB[6]	X	X	X		X	X		X		X		X		X		X		X		X		X		X		X		X	
Urinalysis[6]	X	X	X		X	X		X		X		X		X		X		X		X		X		X		X		X	
Anti-rhGAA Antibody (IgG) Titers/Inhibitory Antibody Monitoring[7]		X				X				X		X		X				X				X				X			
ECG	X	X	X		X	X		X		X				X				X				X				X			
ECHO	X					X				X				X				X				X				X			
Vital Sign Monitoring		X	X		X	X		X		X		X		X		X		X		X		X		X		X		X	
Telemetry Monitoring[8]			X							X				X				X				X				X			
Cyclophosphamide[9]			X							X				X				X				X				X			
Myozyme Infusion			X			X				X		X		X		X		X		X		X		X		X		X	
Pompe PEDI[10]	X																	X								X			
GMFM-66[10]	X																	X								X			
AIMS[10]	X																	X								X			
Ventilator Use Assessment	Continuous Monitoring																												

Table 9-1 Schedule of Assessments – Regimen A ITI Treatment Module (Months 1 Through 6) (continued)

	Month 1									Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4				W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 20	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
Concomitant Medication Monitoring[11]	Continuous Monitoring																												
Concomitant Therapy Monitoring[11]	Continuous Monitoring																												
Adverse Event Monitoring[2]	Continuous Monitoring																												

[1] Includes, but is not limited to, confirmation of CRIM status, documentation of GAA enzyme deficiency, and anti-rhGAA titer levels (see Section 7.1).
[2] At screening/baseline, medical history will include an evaluation of retrospective, related AEs occurring while the patient was receiving Myozyme treatment prior to study entry (Section 9.6).
[3] Blood sample for patient gene mutation analysis must be obtained at baseline. Testing performed prior to informed consent is allowed, provided that written results are provided to the site. If consent is provided, samples also will be obtained from the biological parent(s) at baseline.
[4] Pregnancy testing for female patients of childbearing potential will be repeated on Day 0 if this occurs >14 days after the baseline test. Pregnancy test results must be obtained prior to starting the ITI regimen, and patients with positive test results will be excluded (or withdrawn) from the study.
[5] In addition to the scheduled physical examinations, brief, physical assessments should also be performed prior to the administration of any study medications (Myozyme and cyclophosphamide) to specifically ensure that the patient is clinically stable and can tolerate administration of these agents.
[6] Results of the most recent laboratory tests (obtained on the day of the infusion) should be reviewed by Investigators prior to dosing with cyclophosphamide. Results of the most recent immunoglobulin panel should also be reviewed prior to dosing.
[7] If a patient becomes anti-rhGAA (IgG) positive during the course of the study, he/she will also be tested every 2 months for the presence of inhibitory antibodies to Myozyme.
[8] Patients with cardiomegaly or hypertrophic cardiomyopathy will be admitted to the hospital for all cyclophosphamide infusions and will remain in the hospital for a minimum of 24 hours post-infusion.
[9] Patients should be well-hydrated prior to cyclophosphamide administration, but the patients' cardiac status should be taken into account when determining appropriate amount of hydration.
[10] A visit window of ±7 days will be permitted for the Pompe PEDI, GMFM-66, and AIMS. All remaining study assessments should be conducted at the indicated study visit during the ITI treatment module. Eligible CRIM-negative patients will be followed for a minimum of 18 months on treatment or, if a patient is <6 months of age at the time of enrollment, until the patient is 2 years of age.
[11] All concomitant medications and therapies, including those given as prophylaxis or prior to an infusion, will be recorded in the eCRF.

Note: It is recommended that the Investigator monitor a patient's immunoglobulin levels and consider IVIG administration at a dose of 400 mg/kg, regardless of age, if indicated per the individual Investigator's clinical discretion.

Key: AIMS=Alberta Infantile Motor Scale; BL=baseline/screening; CBC=complete blood count; CK=creatine kinase; CK-MB=creatine kinase – myocardial band; CRIM=cross-reacting immunologic material; D=day; ECG= electrocardiogram; ECHO; echocardiogram; ELISPOT=enzyme-linked immunosorbent spot [assay]; GAA=acid α-glucosidase; GMFM-66=Gross Motor Function Measure-66; IgG=immunoglobulin G; IVIG=intravenous immunoglobulin; PEDI=Pediatric Evaluation of Disability Inventory; rhGAA=Recombinant human acid α-glucosidase; W=week

Table 9-2 Schedule of Assessments – Regimen B ITI Treatment Module (Months 1 Through 6)

	Month 1								Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4			W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
Informed Consent	X																											
Confirmation of Inclusion/Exclusion Criteria[1]	X																											
Demographics	X																											
Medical/Surgical/ Pompe Disease History[2]	X																											
Genetic Mutation Analysis[3]	X																											
Optional Parental GAA Mutation Analysis	X																											
Pregnancy testing[4]	X		X						X				X				X				X				X			
Optional Porta-Catheter Placement	X																											
Physical Examination[5]	X	X	X		X	X		X	X		X		X		X		X		X		X		X		X		X	
Research Immunophenotyping		X			X	X		X									X								X			
Lymphocyte Subpopulation Counts		X			X	X		X									X								X			
Functional T cell Assay (ELISPOT)		X			X	X		X			X						X								X			
Immunoglobulin Panel[6]		X						X			X		X				X				X				X			

Table 9-2 Schedule of Assessments – Regimen B ITI Treatment Module (Months 1 Through 6) (continued)

	Month 1								Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4			W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
CBC with Differential[6]	X	X	X		X	X		X	X		X		X		X		X		X		X		X		X		X	
Chemistry, CK and CK-MB[6]	X	X	X		X	X		X	X		X		X		X		X		X		X		X		X		X	
Urinalysis[6]	X	X	X		X	X		X	X		X		X		X		X		X		X		X		X		X	
Anti-rhGAA Antibody (IgG) Titers/Inhibitory Antibody Monitoring[7]		X				X			X		X		X				X				X				X			
ECG	X	X	X	X	X	X			X				X				X				X				X			
ECHO	X					X			X		X		X				X				X				X			
Vital Sign Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telemetry Monitoring[8]				X	X		X	X																				
Myozyme Infusion			X			X			X		X		X		X		X		X		X		X		X		X	
Rituximab[9,10,11,]				X	X		X	X																				
Methotrexate[12,13]				X			X			X		X		X		X		X		X		X		X		X		X
Pompe PEDI[14]	X																X								X			
GMFM-66[14]	X																X								X			
AIMS[14]	X																X								X			
Ventilator Use Assessment	Continuous Monitoring																											

Table 9-2 Schedule of Assessments – Regimen B ITI Treatment Module (Months 1 Through 6) (continued)

	Month 1								Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4			W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
Concomitant Medication Monitoring[15]	Continuous Monitoring																											
Concomitant Therapy Monitoring[15]	Continuous Monitoring																											
Adverse Event Monitoring[2]	Continuous Monitoring																											

[1] Includes, but is not limited to, confirmation of CRIM status, documentation of GAA enzyme deficiency, and anti-rhGAA titer levels (see Section 7.1).
[2] At screening/baseline, medical history will include an evaluation of retrospective, related AEs occurring while the patient was receiving Myozyme treatment prior to study entry (Section 9.6).
[3] Blood sample for patient gene mutation analysis must be obtained at baseline. Testing performed prior to informed consent is allowed, provided that written results are provided to the site. If consent is provided, samples also will be obtained from the biological parent(s) at baseline.
[4] Pregnancy testing for female patients of childbearing potential will be repeated on Day 0 if this occurs >14 days after the baseline test. Pregnancy test results must be obtained prior to starting the ITI regimen, and patients with positive test results will be excluded (or withdrawn) from the study.
[5] In addition to the scheduled physical examinations, brief, physical assessments should also be performed prior to the administration of any study medications (Myozyme, methotrexate, or rituximab) to ensure that the patient is clinically stable and can tolerate administration of these agents.
[6] Results for the most recent laboratory tests (obtained the preceding day prior to initiating the Myozyme infusion) should be reviewed by Investigators prior to dosing with rituximab and methotrexate. Results of the most recent immunoglobulin panel should also be reviewed prior to dosing.
[7] If a patient becomes anti-rhGAA (IgG) positive during the course of the study, he/she will also be tested every 2 months for the presence of inhibitory antibodies to Myozyme.
[8] Patients with cardiomegaly or hypertrophic cardiomyopathy will be admitted to the hospital for all cyclophosphamide infusions and will remain in the hospital for a minimum of 24 hours post-infusion.
[9] Patients will be admitted to the hospital for all rituximab infusions and will remain in the hospital for a minimum of 24 hours post-infusion. Telemetry will be performed during all rituximab infusions from at least 10 minutes prior to the start of the infusion until at least 2 hours post-infusion.
[10] An optional, additional 4-week cycle of rituximab (up to 4 additional doses) may be administered as described in Section 8.1. This additional cycle must be completed within the first 6 months of the study.
[11] Pre-infusion medication may be given as per rituximab treatment guidelines.
[12] Patients should be well-hydrated prior to methotrexate administration, but the patients' cardiac status should be taken into account when determining appropriate amount of hydration.
[13] Folinic acid supplementation may be given at the discretion of the Investigator beginning 24 hours after the dose of methotrexate.
[14] A visit window of ±7 days will be permitted for the Pompe PEDI, GMFM-66, and AIMS. All remaining study assessments should be conducted at the indicated study visit during the ITI treatment module. Eligible CRIM-negative patients will be followed for a minimum of 18 months on treatment or, if a patient is <6 months of age at the time of enrollment, until the patient is 2 years of age.
[15] All concomitant medications and therapies, including those given as prophylaxis or prior to an infusion, will be recorded in the eCRF.

Note: It is recommended that the Investigator monitor a patient's immunoglobulin levels and consider IVIG administration at a dose of 400 mg/kg, regardless of age, if indicated per the individual Investigator's clinical discretion.

Key: AIMS=Alberta Infantile Motor Scale; BL=baseline/screening; CBC=complete blood count; CK=creatine kinase; CK-MB=creatine kinase – myocardial band; CRIM=cross-reacting immunologic material; D=day; ECG= electrocardiogram; ECHO; echocardiogram; ELISPOT=enzyme-linked immunosorbent spot [assay]; GAA=acid α-glucosidase; GMFM-66=Gross Motor Function Measure-66; IgG=immunoglobulin G; IVIG=intravenous immunoglobulin; PEDI=Pediatric Evaluation of Disability Inventory; rhGAA=Recombinant human acid α-glucosidase; W=week

Table 9-3 Schedule of Assessments – Follow-up Module (Months 7 Through 18)

	Month 7[1]		Month 8[1]		Month 9[1]		Month 10[1]		Month 11[1]		Month 12[1]		Month 13[1]		Month 14[1]		Month 15[1]		Month 16[1]		Month 17[1]		Month 18[1]		EOS[1]	
	W25	W27	W29	W31	W33	W35	W37	W39	W41	W43	W45	W47	W49	W51	W53	W55	W57	W59	W61	W63	W65	W67	W69	W71	W73[2]	W75
	D168	D182	D196	D210	D224	D238	D252	D266	D280	D294	D308	D322	D336	D350	D364	D378	D392	D406	D420	D434	D448	D462	D476	D490	D504	D518
Physical Examination[3]	X		X		X		X		X		X		X		X		X		X		X		X			X
Pregnancy Testing[4]	X		X		X		X		X		X		X		X		X		X		X		X			X
Vital Sign Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Myozyme Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Research Immunophenotyping	X				X				X				X				X				X					X
Lymphocyte Subpopulation Counts	X				X				X				X				X				X					X
Functional T cell Assay (ELISPOT)	X				X				X				X				X				X					X
Immunoglobulin Panel	X				X				X				X				X				X					X
CBC with Differential	X		X		X		X		X		X		X		X		X		X		X		X			X
Chemistry, CK and CK-MB	X		X		X		X		X		X		X		X		X		X		X		X			X
Urinalysis	X		X		X		X		X		X		X		X		X		X		X		X			X
Anti-rhGAA Antibody (IgG) Titers/Inhibitory Antibody Monitoring[5]	X		X		X		X		X		X		X		X		X		X		X		X			X
ECG	X						X						X						X							X
ECHO	X						X						X						X							X

Table 9-3 Schedule of Assessments – Follow-up Module (Months 7 Through 18) (continued)

	Month 7[1]		Month 8[1]		Month 9[1]		Month 10[1]		Month 11[1]		Month 12[1]		Month 13[1]		Month 14[1]		Month 15[1]		Month 16[1]		Month 17[1]		Month 18[1]		EOS[1]	
	W25	W27	W29	W31	W33	W35	W37	W39	W41	W43	W45	W47	W49	W51	W53	W55	W57	W59	W61	W63	W65	W67	W69	W71	W73[2]	W75
	D168	D182	D196	D210	D224	D238	D252	D266	D280	D294	D308	D322	D336	D350	D364	D378	D392	D406	D420	D434	D448	D462	D476	D490	D504	D518
Pompe PEDI							X						X						X							X
GMFM-66							X						X						X							X
AIMS							X						X						X							X
Ventilator Use Monitoring	Continuous Monitoring																									
Concomitant Medication Monitoring	Continuous Monitoring																									
Concomitant Therapy Monitoring	Continuous Monitoring																									
Adverse Event Monitoring	Continuous Monitoring																									

[1] A visit window of ±2 weeks will be permitted for all study assessments during the follow-up module. For Myozyme infusions, the visit window is ±1 week.
[2] Patients who are <2 years of age at their W73 visit should continue in the study until they reach their second (i.e., 2 years of age) birthday. Therefore, these patients should repeat the Schedule of Assessments at W25 and continue following the protocol until they reach this birthday (W75 visit will mimic W25 assessments, W77 visit will mimic W27 assessments, etc.). At the patient's second birthday visit, all End-of-Study (EOS) assessments should be performed for study completion. See Appendix 14.6 for further details.
[3] In addition to the scheduled physical examinations, brief, physical assessments should also be performed prior to the administration of any study medications (Myozyme) to ensure that the patient is clinically stable and can tolerate administration of these agents.
[4] Pregnancy testing will be performed monthly for female patients of childbearing potential, and patients with positive test results will be withdrawn from the study.
[5] If a patient becomes anti-rhGAA (IgG) positive during the course of the study, he/she will also be tested every 2 months for the presence of inhibitory antibodies to Myozyme.

Key: AIMS=Alberta Infantile Motor Scale; CBC=complete blood count; CK=creatine kinase; CK-MB=creatine kinase – myocardial band; D=day; ECG=electrocardiogram; ECHO; echocardiogram; ELISPOT=enzyme-linked immunosorbent spot [assay]; EOS=End-of-Study; GMFM-66=Gross Motor Function Measure-66; IgG=immunoglobulin G; IVIG=intravenous immunoglobulin; PEDI=Pediatric Evaluation and Disability Inventory; rhGAA=Recombinant human acid α-glucosidase; W=week

9.2 Screening/Baseline Assessments

Refer to Table 9-1 and Table 9-2 for the list of study assessments to be conducted at baseline.

9.2.1 Informed Consent

Prior to the start of any screening procedures, the participating physicians (or designated staff) will explain the nature of the study and its risks and benefits to the patient (and/or the patient's legal guardian[s] if the patient is <18 years of age). Each patient (and/or legal guardian[s]) will receive an informed consent form with patient information. Ample time should be allotted for patients/guardians to read the information and ask questions. The patient (and/or legal guardian[s]) will be informed of the right to withdraw from the study at any time, without prejudice.

If the patient and/or legal guardian(s) agree to the patient's participation, the patient (and/or legal guardian[s]) must sign the informed consent form. A signed copy will be provided to the patient (and/or legal guardian[s]), and the original will be retained in the patient's medical chart.

In addition, each biological parent will be asked to provide a blood sample for GAA mutation analysis; a separate informed consent will be obtained for this procedure.

9.2.2 Medical History, Demographics, Eligibility Criteria

A complete medical/surgical/Pompe disease history will be obtained for each patient prior to commencing any study procedures. Specific information will be recorded in the patient's medical chart and the eCRF relating to any prior or existing medical conditions and surgical procedures involving the following systems: Infectious Diseases; Allergic; Metabolic/ Endocrine/Nutritional; Hematopoietic; Musculoskeletal, Dermatologic; Head, Eyes, Ears, Nose, and Throat (HEENT); Breasts; Respiratory; Cardiovascular; Gastrointestinal/Hepatic; Genitourinary/Renal; and Neurologic. All prior history of ventilator use will be collected. The following information will be collected as confirmation of a patient's eligibility according to the study's inclusion/exclusion criteria:

- Clinical signs and symptoms of Pompe disease;
- Family history of Pompe disease;
- Anti-rhGAA titer levels (at least 2 titers obtained at least 1 month apart*; see Section 7.1)
- GAA enzyme deficiency and GAA gene mutations, including method of diagnosis and result(s) (see also Sections 7.1 and 9.2.3);
- CRIM status (see also Sections 7.1 and 9.2.4);

* Only the most recent titer value should be recorded in the eCRF.

- Relevant medical history including any co-existing conditions, as well as retrospective, related AEs (see also Section 9.6);
- Pregnancy status for women of childbearing potential (see also Section 9.4.8).

Additionally, the following demographic data will be collected:

- Gender;
- Date of birth;
- Race/Ethnicity.

9.2.3 Genotyping of the Human Acid Alpha-Glucosidase Gene

DNA will be isolated from peripheral blood samples obtained from patients at baseline for GAA mutation analysis. Note that historical GAA mutation analysis results (performed prior to enrollment) are acceptable, provided that written documentation of the laboratory results is available at the enrolling site. When consent is provided, blood samples also will be obtained at baseline from the patient's biological parent(s) for parental GAA mutation analysis. Using established methods, DNA sequencing will be performed on samples to fully characterize both deleterious mutations and background variation within the GAA gene. All samples will be analyzed by Genzyme, Framingham, MA.

9.2.4 Cross-Reacting Immunologic Material Status Testing

Note that historical CRIM testing results by Western blot analysis (performed prior to enrollment) are acceptable, provided that written documentation of the laboratory results is available at the enrolling site. If, however, CRIM testing results are either not available or the previous testing was performed using a method *other than* Western blot assay on skin fibroblasts, the patient must have (new) CRIM testing performed to confirm eligibility. This testing must be performed according to the procedures outlined in the SOM. The Western blot assay detects the major protein forms of GAA known to exist in the cell, including 110, 95, 76, or 70 kilodalton forms. A patient is considered CRIM positive if the presence of any bands corresponding to the apparent molecular weight of these forms of GAA is detected in samples prepared from patient fibroblasts in the Western blot assay.

9.2.5 Optional Port-a-Catheter

A central venous catheter may be inserted for this study, at the discretion of the Investigator, to facilitate routine and emergency IV treatment. Caution should be used when administering general anesthesia for the placement of a central venous catheter in infantile-onset Pompe disease patients with cardiac hypertrophy (see Section 4.4.1.3).

Cyclophosphamide treatment, which causes a marked and persistent inhibition of cholinesterase activity, potentiates the effect of succinylcholine chloride. If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted.

9.3 Efficacy Measurements

9.3.1 Routine Recombinant Human Acid Alpha-Glucosidase Immunoglobulin G Antibody Testing

Serum samples for anti-rhGAA IgG antibody testing will be obtained prior to each infusion at the time points indicated in Table 9-1 and Table 9-2. This monitoring frequency will exceed the recommended frequency for patients on commercial therapy (i.e., every 3 months), as a more frequent assessment of anti-rhGAA IgG titer is required in this study to fully evaluate the antibody response during and following treatment with immunosuppressants.

Anti-rhGAA IgG testing will be performed by Genzyme. Refer to the SOM for guidelines on the collection and shipment of serum samples.

9.3.2 Inhibitory Antibody Testing

If a patient becomes anti-rhGAA (IgG) positive during the course of the study, he/she will also be tested every 2 months for the presence of inhibitory antibodies (enzyme activity and uptake) to Myozyme. This testing will be done by Genzyme using the serum sample collected for anti-rhGAA IgG antibody testing.

9.3.3 Echocardiogram, Including Left Ventricular Mass Index

M-mode, 2-dimensional, and Doppler mode echocardiography will be performed. The primary cardiac outcome parameters (measured and derived) to be recorded using off-line review include: LVM, LVMI, left ventricular posterior wall thickness, ejection fraction, and shortening fraction.

ECHOs will be performed according to procedures outlined in the SOM and Cardiology Manual, and reviewed by a central cardiologist. A cardiologist at the study site should also review the ECHO in a timely manner for clinical management of the patient.

9.3.4 Ventilator Use

In the event that a patient requires ventilator support (invasive or non-invasive) at any time during the study, the patient and/or the patient's legal guardian(s) will be asked to complete a daily ventilator use diary. The daily ventilator use diary is only required to be completed for patients using ventilator support.

The following data points will be captured in the eCRF: the start date of first ventilator use and the reasons for first ventilator use; the average number of hours of ventilator use/day, biweekly average, collected from the time of first ventilator use and every 2 weeks thereafter (if

applicable) until (1) ventilator support is no longer needed, (2) patient death, or (3) end of the study (whichever occurs first); and the date and reason that ventilator use is no longer needed.

If the patient requires ventilator support on more than 1 occasion during study treatment, the start date, start time, stop date, stop time, and reason for each episode of continuous ventilator support will be recorded, as will the average number of hours of ventilator use/day, measured biweekly average, until (1) ventilator support is no longer needed, (2) patient death, or (3) end of the study (whichever occurs first). If applicable, the date on which tracheostomy was first performed will also be recorded.

9.3.5 Motor Development and Functional Assessments

Gross motor development and function will be assessed through administration of the GMFM-66, AIMS, and the Pompe PEDI. All persons performing these assessments will be trained in order to minimize any test administration variability. Each assessment will also be centrally scored by a trained clinician (e.g., physical therapist). Details of each assessment are provided below and in the SOM.

9.3.5.1 Gross Motor Function Measure

The GMFM-66 (Russell, 2002, *The Gross Motor Function Measure [GMFM-66 & GMFM-88] User's Manual*) will be administered to evaluate changes in motor function. The GMFM-66 is a standardized observational instrument that has been designed and validated to measure change over time in the gross motor abilities of children with cerebral palsy. The GMFM-66 is widely used internationally and is recognized as the gold standard for outcomes assessment in clinical interventions for individuals with cerebral palsy. As the instrument is designed to evaluate change over time in individual patients, there is no age cutoff for administration of the GMFM-66.

The GMFM consists of 66 items organized into 5 categories:

- Lying and Rolling;
- Sitting;
- Crawling and Kneeling;
- Standing;
- Walking, Running, and Jumping.

Items were selected to represent motor functions typically performed by children without motor impairments by 5 years of age. Each item is scored on a 4-point Likert scale (i.e., 0 = cannot do; 1 = initiates [<10% of the task]; 2 = partially completes [10 to <100 % of the task]; 3 = task completion; NT = not tested). The score for each dimension is expressed as a percentage of the maximum score for that dimension. The total score is obtained by adding the percentage scores

for each dimension and dividing the sum by the total number of dimensions. Therefore, each dimension contributes equally to the total score. The validity and reliability of the GMFM-66 were established in patients with cerebral palsy using the GMFM-88, the original 88-item version of the test. The GMFM-66 is comprised of 66 of the original 88 items. The GMFM-88 was validated on 136 children with cerebral palsy, 25 children with acute head injuries, and 34 children without motor delays who ranged in age from 1 month to 4.3 years. The GMFM-66 utilizes a software scoring program called the Gross Motor Ability Estimator (GMAE) that converts the instrument from an ordinal scale to an interval scale based on an individual's responses for the 66 items of the test. This conversion system allows for a more precise estimation of the gross motor abilities of the tested individual. The GMAE scoring system was developed using the results of a Rasch analysis performed on a sample of 537 children with cerebral palsy in Ontario, Canada.

9.3.5.2 Alberta Infantile Motor Scale

The AIMS (Piper, 1994, *Motor Assessment of the Developing Infant*) is an observational measure of infant motor performance from term through independent walking. The AIMS assesses the sequential development of motor milestones in terms of progressive development and integration of antigravity muscle control. An infant is encouraged to demonstrate skills he or she can accomplish spontaneously without the assistance of the examiner. The role of the assessor is to observe and analyze the infant's movements. The AIMS is a norm-referenced test based on age- and sex-stratified normative data. Scores will be adjusted to account for gestational age only for patients whose gestational age is <37 weeks.

The AIMS was normalized using representative samples from the general population. As such, this instrument allows for the comparison of tested children to healthy, same-age peers. The AIMS covers normal motor development in infants from birth to 18 months of age. The test can be used to monitor the progress of a child until he/she successfully achieves the highest level of age-equivalence on the test (18 months of age).

In this study, the AIMS will be administered to all patients at study entry, provided they are at or below the highest level of age-equivalent performance for the test (i.e., independent walking), and the AIMS will continue to be administered to these patients until completion of the study to ascertain whether patients maintain any developmental gains achieved while on Myozyme therapy. Test administration requires 20 to 30 minutes.

9.3.5.3 Pompe Pediatric Evaluation of Disability Inventory

A disease-specific version of the PEDI was developed to assess functional capabilities and performance in children with Pompe disease from 2 months through adolescence (Haley, 2003,

Pediatr Rehabil). All patients will be administered the Pompe PEDI. The Pompe PEDI includes all items from the original PEDI, as well as additional items in the Functional Skills, Mobility, and Self-Care domains to reflect clinically relevant functional skills for children with Pompe disease. Norm-based scoring was developed for these new items, and scoring algorithms for the PEDI have been adjusted to reflect the additional normative data collected for the Pompe PEDI. The patient and/or the patient's legal guardian(s) will complete the Pompe PEDI. Test completion requires approximately 60 minutes. Results are reported as raw score, normative standard score (with standard error), and scaled score (with standard error).

9.4 Safety Measurements

9.4.1 Physical Examination

The physical examination should be performed as specified in the Schedule of Assessments (see Table 9-1, Table 9-2, and Table 9-3). A physical examination will be performed using a standardized form with a checklist of items. Each examination will include height, weight, and head circumference, as well the following assessments: General Appearance, Skin, HEENT, Lymph Nodes, Heart, Lungs, Abdomen, Extremities/Joints, Neurological, Mental Status, and Reflexes.

If clinically significant changes from screening/baseline are noted in physical examinations, the changes will be documented as AEs on the AE eCRF. Clinical significance is defined as any variation in physical findings which has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the parameter returns to screening/baseline levels or until the Investigator determines that follow-up is no longer medically necessary.

9.4.2 Safety Laboratory Assessments

The following hematology, chemistry, and urinalysis parameters will be measured:

- CBC with differential;
- Chemistry: albumin, alkaline phosphatase, ALT, AST, BUN, serum calcium, creatinine, direct and indirect bilirubin, glucose, lactate dehydrogenase, serum phosphorus, potassium, serum sodium, total bilirubin, total protein;
- CK and CK-MB;
- Urinalysis: urine color, specific gravity, pH, protein, glucose, ketones, and blood; microscopy, if clinically indicated.

The Investigator has the discretion to order additional laboratory testing at additional intervals as indicated.

Analysis of blood and urine samples will be performed locally per the site's procedures. Laboratory reports should be reviewed promptly and prior to treatment with any of the study medications to ensure the patient is not experiencing any toxicity and is stable enough to continue the ITI regimen. Particular attention should be given to any changes in serum creatinine, BUN, platelets, white cell count, ALT, AST, or bilirubin, or the presence of red cells in the urine.

The Investigator must indicate if out-of-range laboratory values are either clinically significant or not clinically significant. It is anticipated that some laboratory values may be outside of the normal value range due to the underlying disease. As in routine practice, the Investigators should use their clinical judgment when considering clinical significance. Clinical significance is defined as any variation in laboratory parameters which has medical relevance and may result in an alteration in medical care. If clinically significant laboratory changes from baseline are noted, the changes will be documented as AEs on the AE eCRF. The Investigator will also assess the relationship of all clinically significant out-of-range values to study drugs as being not related, remote/unlikely, possible, probable, or definite. The Investigator will continue to monitor the patient with additional laboratory assessments until (1) values have reached normal range and/or baseline levels, or (2) in the judgment of the Investigator, out-of-range values are not related to the administration of study drug or other protocol-specific procedures.

9.4.3 Electrocardiogram

A standard 12-lead ECG will assess the following: heart rate, rhythm, RR interval, PR interval, QRS complex, QT interval, QTc interval, QRS axis, R voltage V6, S voltage V1, left ventricular hypertrophy criteria, right ventricular hypertrophy criteria, and repolarization changes. The site cardiologist will review all ECGs for clinical management of the patient. A central cardiologist will review the ECG for derivation of study data.

If clinically significant changes from screening/baseline are noted in ECG findings, the changes will be documented as AEs on the AE eCRF. Clinical significance is defined as any variation in ECG findings which has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the parameter returns to screening/baseline levels or until the Investigator determines that follow-up is no longer medically necessary.

9.4.4 Vital Signs

Vital signs, including systolic and diastolic blood pressures (mmHg), heart rate (beats per minute), respiratory rate (breaths/minute), and temperature (°C or °F) will be obtained and recorded at Day -1 and all subsequent visits with Myozyme, cyclophosphamide, rituximab, and/or methotrexate dosing. During each Myozyme infusion, vital signs will be recorded

immediately prior to the infusion, every 30 minutes during the infusion, immediately prior to any change in the infusion rate (if the time point is different), and after completion of the post-infusion observation period (with a window of ±15 minutes for time points after the start of infusion). In the event of an IAR to Myozyme, or if otherwise clinically indicated, additional vital sign measurements should be recorded. Periodic vital sign monitoring will be performed prior to, during and/or after the administration of each immunosuppressant agent (cyclophosphamide, rituximab, methotrexate, IVIG) in accordance with the prescribing information for that agent, and at the discretion of the Investigator as clinically indicated.

If clinically significant changes from baseline or pre-infusion are noted in vital signs, the changes will be documented as AEs on the AE eCRF. Clinical significance is defined as any variation in vital signs which has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the parameter returns to normal range or baseline levels or until the Investigator determines that follow-up is no longer medically necessary.

9.4.5 Electrocardiogram Monitoring by Telemetry

Continuous ECG monitoring by telemetry will be performed on the days of cyclophosphamide infusions for patients on Regimen A who have cardiomegaly or hypertrophic cardiomyopathy, and on the days of rituximab infusions for all patients on Regimen B. Telemetry will be performed for at least 10 minutes prior to the start of the infusion to establish a baseline, and will be obtained continuously until a minimum of 2 hours post-infusion. Telemetry alarms will be set according to pre-defined criteria specified according to the site's SOPs. Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias, and may be adjusted or discontinued in response to any other clinically significant findings, at the discretion of the Investigator. At the discretion of the Investigator, patients who develop clinically significant arrhythmias may also undergo additional cardiac monitoring.

If clinically significant changes from screening/baseline are noted in ECG findings, the changes will be documented as AEs on the AE eCRF. Clinical significance is defined as any variation in ECG findings which has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the parameter returns to screening/baseline levels or until the Investigator determines that follow-up is no longer medically necessary.

9.4.6 Lymphocyte Subpopulation Counts

Blood samples will be collected for lymphocyte subpopulation counts, and shipped to a central laboratory designated by the Immune Tolerance Network for analysis. Procedures for the collection, handling, and shipment of samples are provided in the SOM. Laboratory reports for lymphocyte subpopulation counts will be made available by the central laboratory directly to the

Investigator in such time and manner as to assure appropriate clinical review. Refer to the SOM for further details.

9.4.7 Immunoglobulins Panel

Blood samples will be collected for an immunoglobulin panel. Analysis of immunoglobulin will be performed locally per the site's procedures. The results should be reviewed promptly and prior to treatment with any of the study medications.

The Investigator must indicate if out-of-range values are either clinically significant or not clinically significant. As in routine practice, the Investigators should use their clinical judgment when considering clinical significance. Clinical significance is defined as any variation in these parameters which has medical relevance and may result in an alteration in medical care. If clinically significant changes from baseline are noted in immunoglobulin values, the changes will be documented as AEs on the AE eCRF. The Investigator will also assess the relationship of all clinically significant out-of-range values to study drugs as being not related, remote/unlikely, possible, probable, or definite. The Investigator will continue to monitor the patient with additional assessments until (1) values have reached normal range and/or baseline levels, or (2) in the judgment of the Investigator, out-of-range values are not related to the administration of study drug or other protocol-specific procedures.

9.4.8 Pregnancy Test and Use of Contraception

The immunosuppressant agents administered in this study are known teratogens. Therefore, pregnant and lactating women will be excluded from participation in the study, and other women of childbearing potential should be administered these agents only after due consideration of the potential risks and benefit to the patient.

Female patients of childbearing potential must have a negative pregnancy test prior to starting the ITI regimen. Pregnancy testing will be conducted at baseline and will be repeated on Day 0 if that visit occurs >14 days after the baseline test. Monthly pregnancy testing will be performed for the duration of a patient's participation in the study. In addition, all eligible female patients of childbearing potential and sexually mature males will be advised of the risks associated with immunosuppressant agents, and instructed to use a medically accepted method of contraception throughout the study.

If a patient becomes pregnant anytime during her participation in the study, the patient must be discontinued from the study. Pregnancy will be documented as the reason for study discontinuation. The Investigator must notify Genzyme within 24 hours of first learning of the pregnancy, using the appropriate pregnancy notification form (refer to the SOM). The patient should be followed until the outcome of the pregnancy is known (i.e., delivery, elective

termination, or spontaneous abortion). If a partner of a male patient who has received Myozyme becomes pregnant, Genzyme should be notified and, similarly, the pregnancy should be followed until the outcome is known.

Complications during pregnancy as well as pregnancy outcome, once known, must also be reported to Genzyme within 24 hours of knowledge using the pregnancy outcome form (refer to the SOM). If the pregnancy results in the birth of a child, additional follow-up information may be requested.

Note that pregnancy in and of itself is not an AE or an SAE. Pregnancy should not be entered in the eCRF as an AE unless the Investigator suspects an interaction between the study treatment and the contraceptive method.

9.5 Other Assessments

9.5.1 Research Immunophenotyping

Blood samples will be collected for research immunophenotyping and shipped to a central laboratory designated by the Immune Tolerance Network for analysis. Procedures for the collection, handling, and shipment of samples are provided in the SOM.

9.5.2 Functional T-Cell Assay

Peripheral blood lymphocytes will be collected from whole blood, and shipped under appropriate conditions to the specified central immunology laboratory conducting the enzyme-linked immunosorbent spot (ELISPOT) assay designated by the Immune Tolerance Network. Procedures for collection, handling, and shipment of samples are provided in the SOM.

9.5.3 Testing for Moderate, Severe, or Recurrent Infusion-Associated Reactions

In the event that a patient experiences a moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or recurrent mild (Grade 1) IAR to Myozyme, additional blood samples will be collected and sent to Genzyme for analysis as described in Sections 9.5.3.1 to 9.5.3.3. At the request of Genzyme, after consultation with the Investigator, additional blood samples may be collected for recurrent IARs to Myozyme that are suggestive of a hypersensitivity reaction. Refer to the SOM for guidelines on the collection and shipment of samples. Genzyme GPS-RM should be apprised of sample shipments. Testing is conducted to gain additional information as to individuals' responses to Myozyme, and is not intended as the sole means for clinical management of patients. Suggested guidelines for the management of IARs during the event and pretreatment guidelines are summarized in Appendix 1 of the Myozyme Investigator's Brochure. Skin testing may also be performed, if clinically indicated, as described in Section 9.5.3.4.

9.5.3.1 Complement Activation Testing

In the event that a patient experiences a moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or recurrent mild (Grade 1) IAR to Myozyme, a plasma sample will be drawn within 1 to 2 hours of the event for complement activation testing, when clinically indicated.

At the request of Genzyme, after consultation with the Investigator, a plasma sample for complement activation testing may also be collected for patients with recurrent IARs to Myozyme suggestive of a hypersensitivity reaction.

9.5.3.2 Serum Tryptase Testing

In the event that a patient experiences a moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or recurrent mild (Grade 1) IAR to Myozyme, a serum sample will be drawn within 1 to 2 hours of the event for serum tryptase testing, when clinically indicated.

At the request of Genzyme, after consultation with the Investigator, a serum sample for tryptase testing may also be collected for patients with recurrent IARs to Myozyme suggestive of a hypersensitivity reaction.

9.5.3.3 Serum Anti-Recombinant Human Acid Alpha-Glucosidase Immunoglobulin E Antibody Testing

In the event that a patient experiences a moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or recurrent mild (Grade 1) IAR to Myozyme, the patient should return to the study center no sooner than 3 days following the day of the event to have a serum sample collected that will be tested for anti-rhGAA IgE antibodies, when clinically indicated.

At the request of Genzyme, after consultation with the Investigator, a serum sample for IgE testing may also be collected prior to the next scheduled Myozyme infusion for patients with recurrent IARs to Myozyme suggestive of a hypersensitivity reaction.

9.5.3.4 Skin Testing

Skin testing may be performed locally, following consultation with the Investigator, Sponsor, and ARRB, in patients who experience an IAR to Myozyme that meets the following criteria:

- IAR is assessed as moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4) by the Investigator or is mild (Grade 1) recurrent;

AND

- IAR is suggestive of an IgE-mediated acute-type hypersensitivity reaction, with persistent symptoms of bronchospasm, hypotension, and/or urticaria requiring intervention OR any other signs or symptoms at the discretion of the Investigator or Genzyme.

Refer to the SOM for skin testing procedures.

9.5.3.5 Circulating Immune Complexes

In the event that a patient exhibits evidence of symptoms suggestive of Immune Complex Disease (e.g., proteinuria), serum samples will be obtained and sent to Genzyme for the evaluation of circulating immune complexes, in addition to the testing of prior serum samples that have been archived. Immune complex results will be used as a tool to assist in the clinical evaluation of the patient, and clinical management will not be dependent solely on these results. The patient will continue to be monitored for immune complex symptomatology, and serum samples will continue to be obtained for the evaluation of circulating immune complexes, as appropriate. Consideration for further evaluation of possible immune complex disease (i.e., renal biopsy) will be at the discretion of the Investigator. Refer to the SOM for guidelines on the collection and shipment of serum samples.

9.5.4 Concomitant Medications/Therapies

From the time of informed consent through study completion, all medications and therapies (e.g., tube feeds) to treat AEs, for any long-term disease management, given as prophylaxis for this study, or administered as a pretreatment prior to infusion, will be recorded in the eCRFs.

See also Section 8.4, Concomitant Medication/Therapy.

9.6 Adverse Events

AEs will be assessed at screening/baseline. At every subsequent dosing visit (Myozyme, cyclophosphamide, rituximab, methotrexate, and/or IVIG), the patient will be assessed for any new AEs and changes in the status of any ongoing AEs since the previous visit.

All AEs will be graded according to NCI/CTCAE, Version 3.0 (see Appendix 14.5).

Any signs and symptoms experienced by the patient from the time of signing the informed consent form through the final study visit will be recorded in the eCRF.

Since patients must have received Myozyme treatment prior to study enrollment, an assessment of retrospective, related AEs will be conducted at the screening/baseline visit. Information will be solicited regarding AEs assessed as related (i.e., possibly, probably, or definitely related) to the administration of Myozyme that occurred during commercial Myozyme treatment up to the point of consent for AGLU03707. This retrospective data will be recorded in the eCRFs and will be considered clinical study medical history data. All AEs will then be prospectively captured and recorded for the remainder of the patient's participation in the study. GPS-RM will assess SAEs solicited as part of the retrospective data collection for possible submission to regulatory authorities as clinical study safety reports. Serious, related events will be evaluated based upon local labeling for submission to international regulatory agencies in countries where Myozyme is

approved. Day 1, for the determination of submission due date, will be based upon the day when Genzyme GPS-RM becomes aware of the retrospective SAE.

After completion of the study (18 or 24 months) or early withdrawal from the study, due to potential long-term adverse effects related to the administration of immunosuppressant drugs, it is recommended that physicians report any AEs suggestive of immunosuppressant-induced toxicity to GPS-RM, in addition to the product manufacturer, as a spontaneous report. These data will not be included in the clinical study database, but will be maintained in the GPS-RM database.

9.6.1 Adverse Event Definition

An AE is defined as any undesirable physical, psychological, or behavioral effect experienced by a patient or subject during his/her participation in an investigational study, in conjunction with the use of the drug or biologic, whether or not product-related. This includes any untoward signs or symptoms experienced by the patient from the time of signing of the informed consent form until completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient or subject and/or observed by the Investigator or medical staff;
- Findings at physical examinations;
- Laboratory abnormalities of clinical significance.

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product are not considered AEs after treatment with Myozyme unless they reoccur after the patient has recovered from the preexisting condition or, in the opinion of the Investigator, they represent a clinically significant exacerbation in intensity or frequency.

If a clinically significant worsening from baseline is noted, the changes will be documented as AEs on the AE eCRF. Clinical significance is defined as any variation in signs, symptoms, or testing that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the parameter returns to baseline or until the Investigator determines that follow-up is no longer medically necessary.

All AEs will be noted in the eCRF, with a full description including the nature, date and time of onset and resolution, determination of seriousness, severity, corrective treatment, outcome, and relationship (i.e., not related, remote/unlikely, possibly, probably, or definitely) to Myozyme, cyclophosphamide, rituximab, methotrexate, and/or IVIG, as applicable to the regimen.

9.6.2 Serious Adverse Events

An SAE is any AE that results in any of the following outcomes:

- Death;
- Life-threatening experience;
- Required or prolonged inpatient hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly; or
- Important medical events that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above;
- New invasive ventilator use.

Life-threatening experience: Any AE that places the patient, in the view of the reporter, at immediate risk of death from the AE as it occurred, i.e., does not include an AE that, had it occurred in a more severe form, might have caused death.

Persistent or significant disability/incapacity: Any AE that results in a substantial disruption of a person's ability to conduct normal life functions.

Important medical events that may jeopardize the patient or subject, and may require medical or surgical intervention to prevent one of the outcomes listed above: AEs that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Any new invasive ventilator use: Due to the medical significance of any new ventilator use in this patient population, any new use of invasive ventilator support will be reported as an SAE. If a patient requiring ventilator support becomes ventilator independent, the next instance of invasive ventilator support (if applicable) will be considered a new SAE.

9.6.3 Severity Scoring

The Investigator will be asked to assess the severity of each AE using the following categories: Grade 1, Grade 2, Grade 3, Grade 4, or Grade 5 based on the NCI/CTCAE, Version 3.0 (provided in Appendix 14.5, and available online at http://ctep.cancer.gov/reporting/ctc.html). The CTCAE are also presented in the SOM. AEs not explicitly included in the CTCAE will also be graded according to these definitions:

Grade 1: Mild (intervention/treatment not needed or symptomatic treatment);
Grade 2: Moderate (specific but non-invasive intervention; first line treatment may be given);
Grade 3: Severe (active diagnostic interventions/invasive or more intensive treatment);
Grade 4: Life-threatening or disabling (substantial hazard or risk; major intervention);

Grade 5: Death.

Each event should be evaluated to determine if the event also meets serious criteria (Section 9.6.2). By ICH definition, Grade 4 and 5 events are SAEs and must be reported to Genzyme according to Section 9.6.5.

9.6.4 Infusion-Associated Reactions

IARs are defined as AEs that occur during either the Myozyme infusion or the observation period following the Myozyme infusion which are deemed to be related (i.e., possibly, probably, or definitely) to Myozyme. At the discretion of the Investigator, AEs occurring after completion of the post-infusion observation period for Myozyme that are assessed as related to Myozyme may also be considered IARs. These events should be reported to Genzyme GPS-RM within 24 hours of the Investigator's first knowledge of the event. Refer to Section 9.5.3 for additional testing in the event a patient experiences a moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or recurrent mild (Grade 1) IAR to Myozyme. Suggested guidelines for the management of IARs, and pretreatment prior to subsequent dosing of Myozyme, are summarized in Appendix 1 of the Myozyme Investigator's Brochure.

Those reactions that occur during either the infusion or the post-infusion observation period of cyclophosphamide, methotrexate, rituximab, or IVIG, which are deemed to be related (i.e., probably, possibly, or definitely) to cyclophosphamide, methotrexate, rituximab, or IVIG will be considered AEs, but not IARs.

9.6.5 Adverse Experience and Serious Adverse Experience Reporting

The necessity and time requirements for reporting of AEs to Genzyme or designee and/or regulatory agencies are as follows:

- All SAEs and IARs (non-serious and serious) will be reported within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to the study drug(s). Such communications are to be directed to:

Global Patient Safety and Risk Management
[redacted]
(phone: week days/after hours)
[redacted]

- All SAEs and IARs will include a detailed description of the event(s). Copies of relevant patient records, autopsy reports, and other documents may be requested by and will be sent to Genzyme GPS-RM Department.

Additionally, the Investigator or designee must notify the IRB of any SAE in accordance with the IRB's policy. Depending upon regional requirements, it is the responsibility of either the Investigator or Genzyme to notify the IRB. All unexpected SAEs associated with the use of the study treatment will be reported to appropriate regulatory agencies by Genzyme within the required timeframes.

Any AEs or SAEs experienced by the patient from the time of signing of the informed consent through completion of the final study assessments must be reported as described and recorded in the eCRF. After completion of the final study assessments, all patients must be followed an additional 30 days. At the follow-up assessment, outcome for ongoing AEs and SAEs should be documented in the eCRF as not yet recovered. Ongoing SAEs should, however, continue to be followed (and information reported to GPS-RM) until resolution, until the Investigator deems follow-up is no longer medically necessary, or until the patient is lost to follow-up.

For patients transitioning to commercial Myozyme prior to the 30-day follow-up assessment, follow-up contact should occur prior to the first infusion of commercial Myozyme to assess for ongoing AEs and SAEs. At the 30-day follow-up assessment, outcome for AEs and SAEs ongoing at the time of follow-up contact should be documented in the eCRF. Ongoing SAEs at the time of the 30-day follow-up assessment should continue to be followed (and information reported to GPS-RM) until resolution, until the Investigator deems follow-up is no longer medically necessary, or until the patient is lost to follow-up.

9.7 Study Drug Administration Stopping Rules

The independent ITIRB (Section 12.3) will assemble regularly to review safety data collected from ongoing clinical studies of Myozyme that may necessitate temporary or permanent discontinuation of treatment.

Safety reviews will also occur on an expedited, *ad hoc* basis when 1 of the following scenarios occurs:

- Fatal or life-threatening reaction to study drugs or procedures;
- Occurrence of any other safety-related issues identified by Genzyme GPS-RM that pose a medical concern, including temporary discontinuation of the ITI regimen for any patient, as outlined in Section 7.3.2.

After review, the ITIRB will recommend one of the following:

- Continuation of study drug for all patients in AGLU03707;
- Continuation of study drug (Myozyme, cyclophosphamide, rituximab, methotrexate, and/or IVIG), but with changes for all or selected patients in AGLU03707 (e.g., a change in dose for 1 or more patients; see Section 7.4);

- Discontinuation of study drug (either temporary or permanent) for all or selected patients in AGLU03707.

After considering the ITIRB recommendations, final decisions regarding discontinuation of study drug for all or selected patients in AGLU03707 will be made by the Sponsor.

In the event a significant safety concern arises, the Sponsor may immediately decide to discontinue study drug dosing for all clinical study patients prior to receipt of ITIRB recommendation. Investigational sites will be notified within 24 hours of Genzyme's notification of the event(s).

All appropriate regulatory authorities and IRB(s) will be subsequently notified in the event of temporary or permanent discontinuation of study drug for all or selected patients.

10. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

10.1 Recording of Data

Data will be recorded in the eCRF designed by Genzyme's Department of Biomedical Data Sciences and Informatics and Clinical Research, in collaboration with an electronic data capture (EDC) vendor. Clinical data that are not recorded in the eCRF will be captured and transferred to Genzyme's Department of Biomedical Data Sciences and Informatics.

A Genzyme employee or designee will be responsible for entering patient data in the eCRF for the Pompe PEDI, AIMS, and GMFM-66 only. The central cardiologist will enter all ECHO and ECG data in the eCRFs.

10.2 Data Quality Assurance

Data entered in the eCRF must be verifiable against source documents at the investigational site. A clinical monitor from Genzyme or a representative of Genzyme will manually review the eCRFs against the source documents at the investigational site for validity and completeness. Refer to the Monitor's Manual for further details.

All data captured in the eCRFs will be made available to Genzyme or its designee for data management and analysis. If necessary, the study site will be contacted for corrections and/or clarifications of the data.

10.3 Data Management

Genzyme, working in close collaboration with an EDC vendor, will be responsible for:

- Database creation and validation.

Genzyme will be responsible for:

- eCRF review and data validation.

Prior to finalizing and locking the database, all decisions concerning the inclusion or exclusion of data for each patient will be determined by appropriate medical and statistical personnel. Any and all exclusions related to either safety or efficacy will be documented in patient listings.

11. STATISTICAL METHODS AND PLANNED ANALYSES

Prior to locking the database, all data editing will be complete. The process of database lock and data analysis will follow the SOPs of Genzyme's Department of Biomedical Data Sciences and Informatics. This department also will perform analysis of the data collected from this study.

Statistical analyses of all safety and efficacy measurements will be conducted on all patients who receive Myozyme under this protocol.

All data will be presented in by-patient listings. Graphical displays will be presented as appropriate. Summary statistics will be produced as appropriate and meaningful. Continuous variables will be summarized using descriptive statistics (number [n], mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequencies and percentages.

No statistical testing will be conducted. Missing data will not be imputed using statistical methods.

Safety:

All safety data will be presented in by-patient listings.

The incidence of AEs will be summarized by severity, seriousness, relationship to treatment, and relationship to infusion. Vital signs, physical examination findings, and ECG parameters will be summarized as appropriate. The analyses of clinical laboratory measurements will be based upon the frequency of abnormal values and the frequency of clinically significant abnormal values. Additional immunology measurements which include IgE, serum tryptase, complement activation, and skin testing results will be displayed in by-patient listings as will circulating immune complex detection results.

Efficacy:

All efficacy data will be presented in by-patient listings.

Change from baseline in anti-rhGAA antibody titers and in inhibitory antibody formation (activity and uptake) will be presented. Change from baseline in LVMI, GMFM-66 scores, AIMS scores, and Pompe PEDI scores will also be presented. Summary statistics will be presented where appropriate.

Overall survival will be presented as the proportion of patients alive at the end of the study.

The proportion of patients who were alive and ventilator-free over the course of treatment, time to overall invasive ventilator-dependence, and ventilator-free survival time for patients who were ventilator-free at the onset of the study will be calculated. The overall duration of ventilator

support and the number of hours of ventilator use in the 24 hours preceding each infusion visit for patients who required ventilator use at the onset of the study will also be calculated.

Correlation among genotype, the level of α-glucosidase protein, and the presence of binding, anti-rhGAA IgG, and inhibitory antibodies over time will be explored in by-patient graphical displays, where appropriate.

No statistical sample size calculations will be performed. The sample size is based solely on clinical considerations, as the number of Pompe patients satisfying the inclusion/exclusion criteria is likely to be very small.

12. SPECIAL REQUIREMENTS AND PROCEDURES

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of GCP regulations. These requirements are stated in international regulations such as the ICH Guideline E6 Good Clinical Practice and local regulations such as the US Code of Federal Regulations (CFR) and the European Union (EU) Directive 2001/20/EC and EU Directive 2005/28/EC.

12.1 Institutional and Ethical Review

Before enrollment of patients, this protocol, informed consent form, and relevant supporting information must be reviewed and approved by an IRB or Independent Ethics Committee (IEC) in compliance with ICH and local requirements such as 21 CFR 50 and 56 in the US. Genzyme must receive the letter or certificate of approval from the IRB or IEC prior to delivery of clinical supplies.

12.2 Changes to the Conduct of the Study or Protocol

No change in the study procedures shall be effected without the mutual agreement of the Investigator and Genzyme. All significant changes to this protocol must be documented by signed protocol amendments. If changes to the design of the study are made, the amendment must be submitted to and approved by the IRB or IEC, signed by the Investigator, returned to Genzyme, and submitted to the appropriate regulatory authority according to local regulations before changes can be implemented.

12.3 Immune Tolerance Induction Review Board

An independent ITIRB, consisting of experts in the fields of immunology, rheumatology, transplantation, infectious disease, or oncology will be assembled by Genzyme. The ITIRB will evaluate the safety and efficacy of each of the ITI regimens, as outlined in the ITIRB Charter (which is maintained separately from the study protocol). The ITIRB will review all data available after each patient completes 1 month of treatment on a given ITI regimen, after each patient completes 6 months of treatment on a given ITI regimen, and, if applicable, after the patient completes an optional, additional cycle of rituximab, as well as on an expedited *ad hoc* basis, as outlined in the ITIRB Charter. This review will be conducted separately for each regimen; however, enrollment and ITIRB review may proceed simultaneously for each regimen, i.e., 1 regimen does not need to be evaluated prior to enrolling patients on the other regimen.

The ITIRB will provide recommendations about the risk/benefit profile of the ITI regimens. If a regimen appears to have an acceptable risk/benefit profile after the first patient completes the first month of treatment, enrollment in the regimen may continue. If the regimen appears to have an acceptable risk/benefit profile after the first 3 patients in a given regimen have completed

1 month of treatment, additional patients may be enrolled as they present, or as necessary, to further evaluate the ITI regimen.

The ITIRB may also provide recommendations regarding the following: administration of any additional cycles of rituximab in any single patient; adjustments to a patient's ITI regimen to allow the patient to safely continue in the study while maintaining clinical benefit; and temporary or permanent discontinuation of an ITI regimen if signs of infection or toxicity occur during the study.

Each member of the ITIRB will be a physician and will not be directly involved in the study. Each ITIRB member will be required to sign a contract agreement, which includes a confidentiality and financial disclosure statement, assuring no conflicts of interest as a condition for membership on the board. These documents, along with all members' curricula vitae, will be filed centrally within the study files at Genzyme, Cambridge, MA.

Should any major safety issues arise, the final decision regarding the continuation of any or all patients in the study will be made by the Genzyme GPS-RM Safety Officer, or designee, and the ITIRB. If there are no major safety concerns, patients will continue to receive treatment in the study.

12.4 Allergic Reaction Review Board

An independent ARRB, appointed by Genzyme, may review information pertaining to IARs to Myozyme. The ARRB will serve in a consultancy manner and will provide guidance on IAR management, as outlined in the ARRB Charter (which is maintained separately from the study protocol). In addition, the independent ARRB will be consulted on an *ad hoc* basis as outlined in the ARRB Charter. Communication with the board should be directed to members of the Genzyme GPS-RM group.

The ARRB will consist of at least 1 member with expertise in allergy and/or immunology. Each member of the ARRB will be a physician and will not be directly involved in the study. Each ARRB member will be required to sign a contract agreement, which includes a confidentiality and financial disclosure statement, assuring no conflicts of interest as a condition for membership on the board. These documents, along with all members' curricula vitae, will be filed centrally within the protocol study files at Genzyme, Cambridge, MA.

Should any major safety issues arise, the final decisions regarding the study will be made by the Genzyme GPS-RM Safety Officer, or designee, and the ARRB.

12.5 Investigator's Responsibilities

12.5.1 Patient Informed Consent

For every patient, appropriate informed consent will be obtained prior to the commencement of any study procedures, and will be documented according to national privacy regulations and other state and/or local laws relating to medical information. It is the responsibility of the Investigator to obtain such consent. Investigators will be expected to remain informed of and to ensure that the informed consent form is compliant with all applicable international and national authority regulations for clinical study conduct.

In addition, the biological parents of the patient will be asked to provide consent for GAA mutation analysis.

Genzyme and the Investigator will develop the informed consent form for submission to the IRB or IEC. Upon approval by the IRB or IEC, the Investigator must furnish: (1) a photocopy of the approved informed consent; and (2) the letter stating formal approval has been granted by the IRB or IEC prior to release of clinical supplies.

Patient confidentiality will be maintained to the extent permitted by applicable laws and regulations. It is the responsibility of the Investigator to report results of evaluations to the patient.

12.5.2 Electronic Data Capture

All non-external data, with the exception of the cardiac data and motor function and developmental assessments, will be entered by the site in the eCRFs in the EDC system designed by Genzyme's Department of Biomedical Data Sciences and Informatics and Clinical Research, in collaboration with an EDC vendor. The cardiac data will be entered in the EDC database by the central cardiologist assigned to the study. Refer to the SOM for details. A Genzyme employee or designee will enter the motor function and developmental assessment data into the EDC database. Refer to the SOM for details.

Copies of pertinent records in connection with the study, including patient charts, laboratory data, etc. will be made available to Genzyme on request in a timely manner throughout the course of the study, with due precaution towards protecting patient privacy. Laboratory data that are not entered into the EDC system will be transferred to Genzyme Data Management.

12.5.3 Record Retention

Essential documents will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a

longer period, however, if required by applicable regulatory requirements or by an agreement with Genzyme. It is the responsibility of Genzyme to inform the Investigator/site as to when these documents no longer need to be retained.

Essential documents are those documents that, individually and collectively, permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator, Genzyme, and monitor with the standards of GCP and with all applicable regulatory requirements.

Any or all of the documents should be available for audit by Genzyme or designee and inspection by the regulatory authority.

12.5.4 Monitoring

A representative of Genzyme will visit the Investigator periodically for the purpose of monitoring the progress of this study in accordance with GCP regulations. It is the responsibility of the Investigator to be present or available for consultation during such scheduled monitoring visits. During these routine visits, all data pertaining to a patient's participation in this clinical investigation must be made available to the Monitor.

An audit may be performed at any time during or after completion of the clinical study by Genzyme personnel or their designee. All study-related documentation must be made available to the designated auditor.

In addition, a representative of a regulatory agency may choose to inspect a study site at any time prior to, during, or after completion of the clinical study. A Genzyme representative will be available to assist in the preparation for such an inspection. All pertinent study data should be made available to the regulatory authority for verification, audit, or inspection purposes.

12.5.5 Materials Control

12.5.5.1 Receipt of Clinical Supplies

A POR form, which details the quantity and description of the investigational product, will accompany the shipment of the investigational product from Genzyme to the Investigator or designee. This receipt must be signed, dated, and returned to Genzyme or Genzyme representative by facsimile transmission. A copy of the signed and dated POR form should be retained in the site pharmacy files. Investigators or designees must ensure that the investigational product, while in their possession, is maintained in accordance with Section 8.2.1 of this protocol. Further instructions can be found in the Investigational Product Handling Manual.

12.5.5.2 Disposition of Unused Clinical Study Material

All used Myozyme vials must be maintained at the clinical site until a Genzyme Clinical Research representative or designee performs accountability. After the used Myozyme vials are accounted for, they should be destroyed by the study site, and their destruction should be documented in accordance with the Investigational Product Handling Manual (Disposition Authorization Form). No used Myozyme vials should be destroyed unless authorized by a Genzyme CPRS representative or designee.

All other used clinical study material can be disposed of per site/hospital regulations after proper documentation, using the respective accountability logs. A Genzyme Clinical Research representative will reconcile accountability records on a periodic basis for clinical study materials used throughout the study.

All unused clinical study material at the site must be maintained under adequate storage conditions in a limited-access area. If any unused material remains on site at study completion, the site will be instructed to destroy or return the material to Genzyme only after accountability has been performed by a Genzyme Clinical Research representative and upon completion of the required destruction/return forms as supplied by Genzyme or designee. No product should be destroyed or returned unless authorized by a Genzyme CPRS representative or designee. Further instructions on the disposition of clinical study material can be found in the Investigational Product Handling Manual.

12.5.6 Disclosure of Data

All information obtained during the conduct of this study will be regarded as confidential, and written permission from Genzyme is required prior to disclosing any information relative to this study. Submission to Genzyme for review and comment prior to submission to the publisher will be required at least 30 days prior to submission. This requirement should not be construed as a means of restricting publication, but is intended solely to assure concurrence regarding data, evaluations, and conclusions and to provide an opportunity to share with the Investigator any new and/or unpublished information of which he/she may be unaware.

12.5.7 Clinical Study Report

If deemed appropriate by the Sponsor, an Investigator(s) shall be designated to sign the completed clinical study report at the end of this study.

The signatory Investigator(s) shall be identified by the Sponsor upon the completion of the study, based upon:

- Patient enrollment (i.e., the individual who enrolls the largest number of patients), or
- The individual's participation in the design of the study.

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14. APPENDICES

14.1 Cyclophosphamide United States Prescribing Information

CYTOXAN®

℞ ONLY

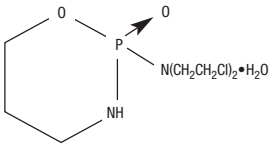
(cyclophosphamide for injection, USP)

CYTOXAN® Tablets

(cyclophosphamide tablets, USP)

DESCRIPTION

CYTOXAN® (cyclophosphamide for injection, USP) is a sterile white powder containing cyclophosphamide monohydrate. CYTOXAN Tablets (cyclophosphamide tablets, USP) are for oral use and contain 25 mg or 50 mg cyclophosphamide (anhydrous). Inactive ingredients in CYTOXAN Tablets are: acacia, FD&C Blue No. 1, D&C Yellow No. 10 Aluminum Lake, lactose, magnesium stearate, starch, stearic acid, and talc. Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is a white crystalline powder with the molecular formula $C_7H_{15}Cl_2N_2O_2P{\bullet}H_2O$ and a molecular weight of 279.1. The chemical name for cyclophosphamide is 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate. Cyclophosphamide is soluble in water, saline, or ethanol and has the following structural formula:



CLINICAL PHARMACOLOGY

Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA.

Cyclophosphamide is well absorbed after oral administration with a bioavailability greater than 75%. The unchanged drug has an elimination half-life of 3 to 12 hours. It is eliminated primarily in the form of metabolites, but from 5 to 25% of the dose is excreted in urine as unchanged drug. Several cytotoxic and noncytotoxic metabolites have been identified in urine and in plasma. Concentrations of metabolites reach a maximum in plasma 2 to 3 hours after an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to an extent greater than 60%. It has not been demonstrated that any single metabolite is responsible for either the therapeutic or toxic effects of cyclophosphamide. Although elevated levels of metabolites of cyclophosphamide have been observed in patients with renal failure, increased clinical toxicity in such patients has not been demonstrated.

INDICATIONS AND USAGE

Malignant Diseases

CYTOXAN, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs. The following malignancies are often susceptible to CYTOXAN treatment:

1. Malignant lymphomas (Stages III and IV of the Ann Arbor staging system), Hodgkin's disease, lymphocytic lymphoma (nodular or diffuse), mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma.
2. Multiple myeloma.
3. Leukemias: Chronic lymphocytic leukemia, chronic granulocytic leukemia (it is usually ineffective in acute blastic crisis), acute myelogenous and monocytic leukemia, acute lymphoblastic (stem-cell) leukemia in children (CYTOXAN given during remission is effective in prolonging its duration).
4. Mycosis fungoides (advanced disease).
5. Neuroblastoma (disseminated disease).
6. Adenocarcinoma of the ovary.
7. Retinoblastoma.
8. Carcinoma of the breast.

Nonmalignant Disease

Biopsy Proven "Minimal Change" Nephrotic Syndrome in Children:

CYTOXAN is useful in carefully selected cases of biopsy proven "minimal change" nephrotic syndrome in children but should not be used as primary therapy. In children whose disease fails to respond adequately to appropriate adrenocorticosteroid therapy or in whom the adrenocorticosteroid therapy produces or threatens to produce intolerable side effects, CYTOXAN may induce a remission. CYTOXAN is not indicated for the nephrotic syndrome in adults or for any other renal disease.

CONTRAINDICATIONS

Continued use of cyclophosphamide is contraindicated in patients with severely depressed bone marrow function. Cyclophosphamide is contraindicated in patients who have demonstrated a previous hypersensitivity to it. See **WARNINGS** and **PRECAUTIONS**.

WARNINGS

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Second malignancies have developed in some patients treated with cyclophosphamide used alone or in association with other antineoplastic drugs and/or modalities. Most frequently, they have been urinary bladder, myeloproliferative, or lymphoproliferative malignancies. Second malignancies most frequently were detected in patients treated for primary myeloproliferative or lymphoproliferative malignancies or nonmalignant disease in which immune processes are believed to be involved pathologically.

In some cases, the second malignancy developed several years after cyclophosphamide treatment had been discontinued. In a single breast cancer trial utilizing two to four times the standard dose of cyclophosphamide in conjunction with doxorubicin a small number of cases of secondary acute myeloid leukemia occurred within two years of treatment initiation. Urinary bladder malignancies generally have occurred in patients who previously had hemorrhagic cystitis. In patients treated with cyclophosphamide-containing regimens for a variety of solid tumors, isolated case reports of secondary malignancies have been published. One case of carcinoma of the renal pelvis was reported in a patient receiving long-term cyclophosphamide therapy for cerebral vasculitis. The possibility of cyclophosphamide-induced malignancy should be considered in any benefit-to-risk assessment for use of the drug.

Cyclophosphamide can cause fetal harm when administered to a pregnant woman and such abnormalities have been reported following cyclophosphamide therapy in pregnant women. Abnormalities were found in two infants and a six-month-old fetus born to women treated with cyclophosphamide. Ectrodactylia was found in two of the three cases. Normal infants have also been born to women treated with cyclophosphamide during pregnancy, including the first trimester. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Development of sterility appears to depend on the dose of cyclophosphamide, duration of therapy, and the state of gonadal function at the time of treatment. Cyclophosphamide-induced sterility may be irreversible in some patients.

Amenorrhea associated with decreased estrogen and increased gonadotropin secretion develops in a significant proportion of women treated with cyclophosphamide. Affected patients generally resume regular menses within a few months after cessation of therapy. Girls treated with cyclophosphamide during prepubescence generally develop secondary sexual characteristics normally and have regular menses. Ovarian fibrosis with apparently complete loss of germ cells after prolonged cyclophosphamide treatment in late prepubescence has been reported. Girls treated with cyclophosphamide during prepubescence subsequently have conceived.

Men treated with cyclophosphamide may develop oligospermia or azoospermia associated with increased gonadotropin but normal testosterone secretion. Sexual potency and libido are unimpaired in these patients. Boys treated with cyclophosphamide during prepubescence develop secondary sexual characteristics normally, but may have oligospermia or azoospermia and increased gonadotropin secretion. Some degree of testicular atrophy may occur. Cyclophosphamide-induced azoospermia is reversible in some patients, though the reversibility may not occur for several years after cessation of therapy. Men temporarily rendered sterile by cyclophosphamide have subsequently fathered normal children.

Urinary System

Hemorrhagic cystitis may develop in patients treated with cyclophosphamide. Rarely, this condition can be severe and even fatal. Fibrosis of the urinary bladder, sometimes extensive, also may develop with or without accompanying cystitis. Atypical urinary bladder epithelial cells may appear in the urine. These adverse effects appear to depend on the dose of cyclophosphamide and the duration of therapy. Such bladder injury is thought to be due to cyclophosphamide metabolites excreted in the urine. Forced fluid intake helps to assure an ample output of urine, necessitates frequent voiding, and reduces the time the drug remains in the bladder. This helps to prevent cystitis. Hematuria usually resolves in a few days after cyclophosphamide treatment is stopped, but it may persist. Medical and/or surgical supportive treatment may be required, rarely, to treat protracted cases of severe hemorrhagic cystitis. It is usually necessary to discontinue cyclophosphamide therapy in instances of severe hemorrhagic cystitis.

Cardiac Toxicity

Although a few instances of cardiac dysfunction have been reported following use of recommended doses of cyclophosphamide, no causal relationship has been established. Acute cardiac toxicity has been reported with doses as low as 2.4 g/m^2 to as high as 26 g/m^2, usually as a portion of an intensive antineoplastic multi-drug regimen or in conjunction with transplantation procedures. In a few instances with high doses of cyclophosphamide, severe, and sometimes fatal, congestive heart failure has occurred after the first cyclophosphamide dose. Histopathologic examination has primarily shown hemorrhagic myocarditis. Hemopericardium has occurred secondary to hemorrhagic myocarditis and myocardial necrosis. Pericarditis has been reported independent of any hemopericardium.

No residual cardiac abnormalities, as evidenced by electrocardiogram or echocardiogram appear to be present in patients surviving episodes of apparent cardiac toxicity associated with high doses of cyclophosphamide.

Cyclophosphamide has been reported to potentiate doxorubicin-induced cardiotoxicity.

Infections

Treatment with cyclophosphamide may cause significant suppression of immune responses. Serious, sometimes fatal, infections may develop in severely immunosuppressed patients. Cyclophosphamide treatment may not be indicated, or should be interrupted, or the dose reduced, in patients who have or who develop viral, bacterial, fungal, protozoan, or helminthic infections.

Other

Anaphylactic reactions have been reported; death has also been reported in association with this event. Possible cross-sensitivity with other alkylating agents has been reported.

PRECAUTIONS

General

Special attention to the possible development of toxicity should be exercised in patients being treated with cyclophosphamide if any of the following conditions are present.

1. Leukopenia
2. Thrombocytopenia
3. Tumor cell infiltration of bone marrow
4. Previous X-ray therapy
5. Previous therapy with other cytotoxic agents
6. Impaired hepatic function
7. Impaired renal function

Laboratory Tests

During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should be monitored regularly to determine the degree of hematopoietic suppression. Urine should also be examined regularly for red cells which may precede hemorrhagic cystitis.

Drug Interactions

The rate of metabolism and the leukopenic activity of cyclophosphamide reportedly are increased by chronic administration of high doses of phenobarbital.

The physician should be alert for possible combined drug actions, desirable or undesirable, involving cyclophosphamide even though cyclophosphamide has been used successfully concurrently with other drugs, including other cytotoxic drugs.

Cyclophosphamide treatment, which causes a marked and persistent inhibition of cholinesterase activity, potentiates the effect of succinylcholine chloride.

If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted.

Adrenalectomy

Since cyclophosphamide has been reported to be more toxic in adrenalectomized dogs, adjustment of the doses of both replacement steroids and cyclophosphamide may be necessary for the adrenalectomized patient.

Wound Healing

Cyclophosphamide may interfere with normal wound healing.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

See **WARNINGS** for information on carcinogenesis, mutagenesis, and impairment of fertility.

Pregnancy

Pregnancy Category D

See **WARNINGS**.

Nursing Mothers

Cyclophosphamide is excreted in breast milk. Because of the potential for serious adverse reactions and the potential for tumorigenicity shown for cyclophosphamide in humans, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety profile of CYTOXAN (cyclophosphamide) in pediatric patients is similar to that of the adult population (see **ADVERSE REACTIONS**).

Geriatric Use

Insufficient data from clinical studies of CYTOXAN for malignant lymphoma, multiple myeloma, leukemia, mycosis fungoides, neuroblastoma, retinoblastoma, and breast carcinoma are available for patients 65 years of age and older to determine whether they respond differently than younger patients. In two clinical trials in which cyclophosphamide was compared with paclitaxel, each in combination with cisplatin, for the treatment of advanced ovarian carcinoma, 154 (28%) of 552 patients who received cyclophosphamide plus cisplatin were 65 years or older. Subset analyses (<65 versus >65 years) from these trials, published reports of clinical trials of cyclophosphamide-containing regimens in breast cancer and non-Hodgkin's lymphoma, and postmarketing experience suggest that elderly patients may be more susceptible to cyclophosphamide toxicities. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and adjusting as necessary based on patient response (see **DOSAGE AND ADMINISTRATION: Treatment of Malignant Diseases**).

ADVERSE REACTIONS

Information on adverse reactions associated with the use of CYTOXAN (cyclophosphamide) is arranged according to body system affected or type of reaction. The adverse reactions are listed in order of decreasing incidence. The most serious adverse reactions are described in the **WARNINGS** section.

Reproductive System
See **WARNINGS** for information on impairment of fertility.

Digestive System
Nausea and vomiting commonly occur with cyclophosphamide therapy. Anorexia and, less frequently, abdominal discomfort or pain and diarrhea may occur. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration and jaundice occurring during therapy. These adverse drug effects generally remit when cyclophosphamide treatment is stopped.

Skin and Its Structures
Alopecia occurs commonly in patients treated with cyclophosphamide. The hair can be expected to grow back after treatment with the drug or even during continued drug treatment, though it may be different in texture or color. Skin rash occurs occasionally in patients receiving the drug. Pigmentation of the skin and changes in nails can occur. Very rare reports of Stevens-Johnson syndrome and toxic epidermal necrolysis have been received during postmarketing surveillance; due to the nature of spontaneous adverse event reporting, a definitive causal relationship to cyclophosphamide has not been established.

Hematopoietic System
Leukopenia occurs in patients treated with cyclophosphamide, is related to the dose of drug, and can be used as a dosage guide. Leukopenia of less than 2000 cells/mm^3 develops commonly in patients treated with an initial loading dose of the drug, and less frequently in patients maintained on smaller doses. The degree of neutropenia is particularly important because it correlates with a reduction in resistance to infections. Fever without documented infection has been reported in neutropenic patients.

Thrombocytopenia or anemia develop occasionally in patients treated with CYTOXAN. These hematologic effects usually can be reversed by reducing the drug dose or by interrupting treatment. Recovery from leukopenia usually begins in 7 to 10 days after cessation of therapy.

Urinary System
See **WARNINGS** for information on cystitis and urinary bladder fibrosis.

Hemorrhagic ureteritis and renal tubular necrosis have been reported to occur in patients treated with cyclophosphamide. Such lesions usually resolve following cessation of therapy.

Infections
See **WARNINGS** for information on reduced host resistance to infections.

Carcinogenesis
See **WARNINGS** for information on carcinogenesis.

Respiratory System
Interstitial pneumonitis has been reported as part of the postmarketing experience. Interstitial pulmonary fibrosis has been reported in patients receiving high doses of cyclophosphamide over a prolonged period.

Other
Anaphylactic reactions have been reported; death has also been reported in association with this event. Possible cross-sensitivity with other alkylating agents has been reported. SIADH (syndrome of inappropriate ADH secretion) has been reported with the use of cyclophosphamide. Malaise and asthenia have been reported as part of the postmarketing experience.

OVERDOSAGE

No specific antidote for cyclophosphamide is known. Overdosage should be managed with supportive measures, including appropriate treatment for any concurrent infection, myelosuppression, or cardiac toxicity should it occur.

DOSAGE AND ADMINISTRATION

Treatment of Malignant Diseases
Adults and Children
When used as the only oncolytic drug therapy, the initial course of CYTOXAN for patients with no hematologic deficiency usually consists of 40 to 50 mg/kg given intravenously in divided doses over a period of 2 to 5 days. Other intravenous regimens include 10 to 15 mg/kg given every 7 to 10 days or 3 to 5 mg/kg twice weekly.

Oral CYTOXAN dosing is usually in the range of 1 to 5 mg/kg/day for both initial and maintenance dosing.

Many other regimens of intravenous and oral CYTOXAN have been reported. Dosages must be adjusted in accord with evidence of antitumor activity and/or leukopenia. The total leukocyte count is a good, objective guide for regulating dosage. Transient decreases in the total white blood cell count to 2000 cells/mm^3 (following short courses) or more persistent reduction to 3000 cells/mm^3 (with continuing therapy) are tolerated without serious risk of infection if there is no marked granulocytopenia.

When CYTOXAN is included in combined cytotoxic regimens, it may be necessary to reduce the dose of CYTOXAN as well as that of the other drugs.

CYTOXAN and its metabolites are dialyzable although there are probably quantitative differences depending upon the dialysis system being used. Patients with compromised renal function may show some measurable changes in pharmacokinetic parameters of CYTOXAN metabolism, but there is no consistent evidence indicating a need for CYTOXAN dosage modification in patients with renal function impairment.

Treatment of Nonmalignant Diseases
Biopsy Proven "Minimal Change" Nephrotic Syndrome In Children
An oral dose of 2.5 to 3 mg/kg daily for a period of 60 to 90 days is recommended. In males, the incidence of oligospermia and azoospermia increases if the duration of CYTOXAN treatment exceeds 60 days. Treatment beyond 90 days increases the probability of sterility. Adrenocorticosteroid therapy may be tapered and discontinued during the course of CYTOXAN therapy. See **PRECAUTIONS** concerning hematologic monitoring.

Preparation and Handling of Solutions
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Add the diluent to the vial and shake it vigorously to dissolve. If the powder fails to dissolve immediately and completely, it is advisable to allow the vial to stand for a few minutes. Use the quantity of diluent shown below to constitute the product:

Dosage Strength	CYTOXAN Contains Cyclophosphamide Monohydrate	Quantity of Diluent
500 mg	534.5 mg	25 mL
1 g	1069.0 mg	50 mL
2 g	2138.0 mg	100 mL

For Direct Injection
CYTOXAN should be prepared for parenteral use by adding 0.9% sterile sodium chloride solution. Solutions of CYTOXAN may be injected intravenously, intramuscularly, intraperitoneally, or intrapleurally if constituted by adding 0.9% sterile sodium chloride solution.

For Infusion
CYTOXAN (cyclophosphamide) may be prepared for parenteral use by infusion using any of the following methods:

1. CYTOXAN constituted with 0.9% sterile sodium chloride may be infused without further dilution.
2. CYTOXAN constituted with 0.9% sterile sodium chloride may be infused following further dilution in the following:
   Dextrose Injection, USP (5% dextrose)
   Dextrose and Sodium Chloride Injection, USP (5% dextrose and 0.9% sterile sodium chloride)
   5% Dextrose and Ringer's Injection
   Lactated Ringer's Injection, USP
   Sodium Chloride Injection, USP (0.45% sterile sodium chloride)
   Sodium Lactate Injection, USP (1/6 molar sodium lactate)
3. CYTOXAN sterile powder may be prepared for parenteral use by infusion by adding Sterile Water for Injection, USP. *CYTOXAN, constituted in water, is hypotonic and should not be injected directly.* Prior to infusion, solutions of CYTOXAN sterile powder constituted in Sterile Water for Injection, USP must be further diluted in one of the following:
   Dextrose Injection, USP (5% dextrose)
   Dextrose and Sodium Chloride Injection, USP (5% dextrose and 0.9% sterile sodium chloride)
   5% Dextrose and Ringer's Injection
   Lactated Ringer's Injection, USP
   Sodium Chloride Injection, USP (0.45% sterile sodium chloride)
   Sodium Lactate Injection, USP (1/6 molar sodium lactate)

Stability of Constituted Parenteral Solutions
CYTOXAN (prepared for either direct injection or infusion) is chemically and physically stable for 24 hours at room temperature or for six days in the refrigerator; it does not contain any antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions.

The osmolarities of solutions of CYTOXAN constituted with water and 0.9% sterile sodium chloride solution are found in the following table:

CYTOXAN and Diluent	mOsm/L
5 mL water per 100 mg cyclophosphamide (anhydrous)	74
5 mL 0.9% sterile sodium chloride solution per 100 mg cyclophosphamide (anhydrous)	374

Isotonic 0.9% sterile sodium chloride solution has an osmolarity of 289 mOsm/L.

For Oral Administration
Extemporaneous liquid preparations of CYTOXAN for oral administration may be prepared by dissolving CYTOXAN in Aromatic Elixir, N.F. Such preparations should be stored under refrigeration in glass containers and used within 14 days.

HOW SUPPLIED

CYTOXAN® (cyclophosphamide for injection, USP) contains cyclophosphamide monohydrate and is supplied in vials for single-dose use.

CYTOXAN (cyclophosphamide for injection, USP).
U.S. Patent No. 4,537,883
NDC 0015-0502-41 500 mg vial, carton of 1
NDC 0015-0505-41 1.0 g vial, carton of 1
NDC 0015-0506-41 2.0 g vial, carton of 1

Store vials at or below 77° F (25° C). During transport or storage of CYTOXAN vials, temperature influences can lead to melting of the active ingredient, cyclophosphamide. Vials containing melted substance can be visually differentiated. Melted cyclophosphamide is a clear or yellowish viscous liquid usually found as a connected phase or in droplets in the affected vials. Do not use CYTOXAN vials if there are signs of melting.

CYTOXAN® Tablets, 25 mg, and CYTOXAN Tablets, 50 mg, are white tablets with blue flecks containing 25 mg and 50 mg cyclophosphamide (anhydrous), respectively.

CYTOXAN Tablets (cyclophosphamide tablets, USP).
NDC 0015-0503-01 50 mg, bottles of 100
NDC 0015-0504-01 25 mg, bottles of 100

Store tablets at or below 77°F (25°C); tablets will withstand brief exposure to temperatures up to 86°F (30°C), but should be protected from temperatures above 86°F (30°C).

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing CYTOXAN sterile powder for injection, or bottles containing CYTOXAN tablets. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

REFERENCES

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2. Recommendations for the safe handling of parenteral antineoplastic drugs. Washington, DC: Division of Safety, National Institutes of Health; 1983. US Dept of Health and Human Services, Public Health Service publication NIH 83-2621.
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Vials Manufactured by:
Baxter Healthcare Corporation
Deerfield, Illinois 60015 USA

Vials Made in Germany

Vials Distributed and Tablets Manufactured by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543

Tablets Made in Italy

Bristol-Myers Squibb Company

H4-B0001-09-05
Revised September 2005

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USA 5638 0612 C 669

14.2 Rituximab United States Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Rituxan safely and effectively. See full prescribing information for Rituxan.

Rituxan (rituximab)
Injection for Intravenous Use
Initial U.S. Approval: 1997

WARNING: FATAL INFUSION REACTIONS, TUMOR LYSIS SYNDROME (TLS), SEVERE MUCOCUTANEOUS REACTIONS, and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

*See **full prescribing information** for complete boxed warning.*

- **Fatal infusion reactions within 24 hours of Rituxan infusion occur; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue Rituxan infusion for severe reactions (5.1).**
- **Tumor lysis syndrome (5.2).**
- **Severe mucocutaneous reactions, some with fatal outcomes (5.3).**
- **PML resulting in death (5.4).**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, PML (5.4) 09/2008

----------INDICATIONS AND USAGE----------

Rituxan is a CD20-directed cytolytic antibody indicated for the treatment of the following:

- Non-Hodgkin's Lymphoma (NHL) (1.1)
- Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies (1.2)

----------DOSAGE AND ADMINISTRATION----------

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

- The dose for NHL is 375 mg/m^2 (2.1).
- The dose as a component of Zevalin® (Ibritumomab tiuxetan) Therapeutic Regimen is 250 mg/m^2 (2.2).
- The dose for Rheumatoid Arthritis is two-1000 mg IV infusions separated by 2 weeks in combination with methotrexate. Methylprednisolone 100 mg IV or equivalent glucocorticoid is recommended 30 minutes prior to each infusion (2.3).

----------DOSAGE FORMS AND STRENGTHS----------

- 100 mg/10 mL and 500 mg/50 mL solution in a single-use vial (3).

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

- Tumor lysis syndrome – administer prophylaxis and monitor renal function (5.2).
- PML - monitor neurologic function. Discontinue Rituxan (5.4).
- Hepatitis B reactivation with fulminant hepatitis, sometimes fatal – screen high risk patients and monitor HBV carriers during and several months after therapy. Discontinue Rituxan if reactivation occurs (5.5).
- Cardiac arrhythmias and angina can occur and can be life threatening. Monitor patients with these conditions closely (5.7).
- Bowel obstruction and perforation - evaluate complaints of abdominal pain (5.9).
- Do not administer live virus vaccines prior to or during Rituxan (5.10).
- Monitor CBC at regular intervals for severe cytopenias (5.11, 6.1).

----------ADVERSE REACTIONS----------

- Non-Hodgkin's Lymphoma (NHL) - Common adverse reactions (≥25%) in clinical trials were: infusion reactions, fever, lymphopenia, chills, infection and asthenia (6.1).
- Rheumatoid Arthritis (RA) - Common adverse reactions (≥5%): hypertension, nausea, upper respiratory tract infection, arthralgia, pruritus, and pyrexia (6.2). Other important adverse reactions include infusion reactions, serious infections, and cardiovascular events (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Renal toxicity when used in combination with cisplatin (5.8).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Limited human data; B-cell lymphocytopenia occurred in infants exposed in utero (8.1).
- Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: FATAL INFUSION REACTIONS, TUMOR LYSIS SYNDROME (TLS), SEVERE MUCOCUTANEOUS REACTIONS, and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

Infusion Reactions
Rituxan administration can result in serious, including fatal infusion reactions. Deaths within 24 hours of Rituxan infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Carefully monitor patients during infusions. Discontinue Rituxan infusion and provide medical treatment for Grade 3 or 4 infusion reactions [*see Warnings and Precautions (5.1), Adverse Reactions (6.1)*].

Tumor Lysis Syndrome (TLS)
Acute renal failure requiring dialysis with instances of fatal outcome can occur in the setting of TLS following treatment of non-Hodgkin's lymphoma (NHL) patients with Rituxan [*see Warnings and Precautions (5.2), Adverse Reactions (6)*].

Severe Mucocutaneous Reactions
Severe, including fatal, mucocutaneous reactions can occur in patients receiving Rituxan [*see Warnings and Precautions (5.3), Adverse Reactions (6)*].

Progressive Multifocal Leukoencephalopathy (PML)
JC virus infection resulting in PML and death can occur in patients receiving Rituxan [*see Warnings and Precautions (5.4), Adverse Reactions (6.4)*].

1 INDICATIONS AND USAGE

1.1 Non–Hodgkin's Lymphoma (NHL)

Rituxan® (rituximab) is indicated for the treatment of patients with:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with CVP chemotherapy
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line CVP chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens

1.2 Rheumatoid Arthritis

Rituxan® (rituximab) in combination with methotrexate is indicated to reduce signs and symptoms and to slow the progression of structural damage in adult patients with moderately-to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

2 DOSAGE AND ADMINISTRATION

2.1 Administration

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

Premedicate before each infusion [*see Dosage and Administration (2.5)*]. Administer only as an intravenous infusion [*see Dosage and Administration (2.5)*].

- **First Infusion**: Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
- **Subsequent Infusions**: Initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.
- Interrupt the infusion or slow the infusion rate for infusion reactions [*see Boxed Warning, Warnings and Precautions (5.1)*]. Continue the infusion at one-half the previous rate upon improvement of symptoms.

2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)

The recommended dose is 375 mg/m^2 as an intravenous infusion according to the following schedules:

- **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**
  Administer once weekly for 4 or 8 doses.
- **Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**
  Administer once weekly for 4 doses.
- **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**
  Administer on Day 1 of each cycle of CVP chemotherapy, for up to 8 doses.
- **Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy**
  Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.
- **Diffuse Large B-Cell NHL**
  Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

2.3 Recommended Dose as a Component of Zevalin®

- Infuse rituximab 250 mg/m^2 within 4 hours prior to the administration of Indium-111-(In-111-) Zevalin and within 4 hours prior to the administration of Yttrium-90- (Y-90-) Zevalin.

- Administer Rituxan and In-111-Zevalin 7-9 days prior to Rituxan and Y-90- Zevalin.
- Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

2.4 Recommended Dose for Rheumatoid Arthritis

- Two-1000 mg intravenous infusions separated by 2 weeks.
- Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions. Safety and efficacy of retreatment have not been established in controlled trials [*see Warnings and Precautions (5.14)*].
- Rituxan is given in combination with methotrexate.

2.5 Recommended Concomitant Medications

Premedicate before each infusion with acetaminophen and an antihistamine.

2.6 Preparation for Administration

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use vial if particulates or discoloration is present. Withdraw the necessary amount of Rituxan and dilute to a final concentration of 1 to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Do not mix or dilute with other drugs. Discard any unused portion left in the vial.

3 DOSAGE FORMS AND STRENGTHS

100 mg/10 mL single-use vial
500 mg/50 mL single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

Rituxan can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes. Rituxan-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, or anaphylactoid events.

Premedicate patients with an antihistamine and acetaminophen prior to dosing. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, consider resumption of the infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who

experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥ 25,000/mm^3). [*See Boxed Warning, Warnings and Precautions (5.7), Adverse Reactions (6.1)*.]

5.2 Tumor Lysis Syndrome (TLS)

Rapid reduction in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia, can occur within 12–24 hours after the first infusion. Fatal TLS cases have occurred after administration of Rituxan. A high number of circulating malignant cells (≥ 25,000/mm^3) or high tumor burden confers a greater risk of TLS after rituximab. Consider prophylaxis for TLS in patients at high risk. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. [*See Boxed Warning*.]

5.3 Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituxan. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has varied from 1–13 weeks following Rituxan exposure. Discontinue Rituxan in patients who experience a severe mucocutaneous reaction. The safety of readministration of Rituxan to patients with severe mucocutaneous reactions has not been determined. [*See Boxed Warning, Adverse Reactions (6.1, 6.4)*.]

5.4 Progressive Multifocal Leukoencephalopathy (PML)

JC virus infection resulting in PML and death can occur in Rituxan-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of Rituxan.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue Rituxan and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML. [*See Boxed Warning, Adverse Reactions (6.4)*.]

5.5 Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with Rituxan. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of Rituxan and approximately one month after the last dose.

Screen patients at high risk of HBV infection before initiation of Rituxan. Closely monitor carriers of hepatitis B for clinical and laboratory signs of active HBV infection for several months following Rituxan therapy. Discontinue Rituxan and any concomitant chemotherapy in patients who develop viral hepatitis, and institute appropriate treatment including antiviral therapy. Insufficient data exist regarding the safety of resuming Rituxan in patients who develop hepatitis subsequent to HBV reactivation. [*See Adverse Reactions (6.4)*.]

5.6 Other Viral Infections

The following additional serious viral infections, either new, reactivated, or exacerbated, have been identified in clinical studies or postmarketing reports. The majority of patients received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred as late as one year following discontinuation of Rituxan and have resulted in death. [*See Adverse Reactions (6.1, 6.4)*.]

5.7 Cardiovascular

Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of Rituxan for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina. [*See Adverse Reactions (6.4)*.]

5.8 Renal

Severe, including fatal, renal toxicity can occur after Rituxan administration in patients with hematologic malignancies. Renal toxicity has occurred in patients with high numbers of circulating malignant cells ($\geq 25{,}000/mm^3$) or high tumor burden who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and Rituxan is not an approved treatment regimen. Use extreme caution if this non-approved combination is used in clinical trials and monitor closely for signs of renal failure. Consider discontinuation of Rituxan for patients with a rising serum creatinine or oliguria.

5.9 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving Rituxan in combination with chemotherapy. In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1–77) days in patients with NHL. Perform a thorough diagnostic evaluation and institute appropriate treatment for complaints of abdominal pain, especially early in the course of Rituxan therapy. [*See Adverse Reactions (6.4)*.]

5.10 Immunization

The safety of immunization with live viral vaccines following Rituxan therapy has not been studied and vaccination with live virus vaccines is not recommended. Physicians should review the vaccination status of patients with RA being considered for Rituxan treatment and follow the Centers for Disease Control and Prevention (CDC) guidelines for adult vaccination with non-live vaccines intended to prevent infectious disease prior to therapy.

For NHL patients, the benefits of primary or booster vaccinations should be weighted against the risks of delay in initiation of Rituxan therapy.

5.11 Laboratory Monitoring

Because Rituxan binds to all CD20-positive B lymphocytes (malignant and nonmalignant), obtain complete blood counts (CBC) and platelet counts at regular intervals during Rituxan therapy and more frequently in patients who develop cytopenias [*see Adverse Reactions (6.1)*]. The duration of cytopenias caused by Rituxan can extend months beyond the treatment period.

5.12 Concomitant Use with Biologic Agents and Disease Modifying Anti-Rheumatic Drugs (DMARDS) other than Methotrexate in RA

Limited data are available on the safety of the use of biologic agents or DMARDs other than methotrexate in patients exhibiting peripheral B-cell depletion following treatment with rituximab. Observe patients closely for signs of infection if biologic agents and/or DMARDs are used concomitantly.

5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists

While efficacy of Rituxan was supported in two well-controlled trials in patients with RA with prior inadequate responses to non-biologic DMARDs, a favorable risk benefit relationship has not been established in this population. The use of Rituxan in patients with RA who have not had prior inadequate response to one or more TNF antagonists is not recommended [*see Clinical Studies (14.5)*].

5.14 Retreatment in Patients with RA

Safety and efficacy of retreatment have not been established in controlled trials. A limited number of patients have received two to five courses (two infusions per course) of treatment in an uncontrolled setting. In clinical trials in patients with RA, most of the patients who received additional courses did so 24 weeks after the previous course and none were retreated sooner than 16 weeks.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Infusion reactions [*see Warnings and Precautions (5.1)*]
- Tumor lysis syndrome [*see Warnings and Precautions (5.2)*]
- Mucocutaneous reactions [*see Warnings and Precautions (5.3)*]
- Progressive multifocal leukoencephalopathy [*see Warnings and Precautions (5.4)*]
- Hepatitis B reactivation with fulminant hepatitis [*see Warnings and Precautions (5.5)*]
- Other viral infections [*see Warnings and Precautions (5.6)*]
- Cardiac arrhythmias [*see Warnings and Precautions (5.7)*]
- Renal toxicity [*see Warnings and Precautions (5.8)*]
- Bowel obstruction and perforation [*see Warnings and Precautions (5.9)*]

The most common adverse reactions of Rituxan (incidence ≥ 25%) observed in patients with NHL are infusion reactions, fever, chills, infection, asthenia, and lymphopenia.

The most important serious adverse reactions of Rituxan are infusion reactions, tumor lysis syndrome, mucocutaneous toxicities, hepatitis B reactivation with fulminant hepatitis, PML, other viral infections, cardiac arrhythmias, renal toxicity, and bowel obstruction and perforation.

6.1 Clinical Trials Experience Non-Hodgkin's Lymphoma

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Rituxan in 1606 patients, with exposures ranging from a single infusion up to 6–8 months. Rituxan was studied in both single-agent and active-controlled trials (n = 356 and n= 1250). These data were obtained in adults with low-grade, follicular, or DLBCL NHL. Most patients received Rituxan as an infusion of 375 mg/m^2 per infusion, given as a single agent weekly for up to 8 doses, in combination with chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses.

Infusion Reactions

In the majority of patients with NHL, infusion reactions consisting of fever, chills/rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension occurred during the first Rituxan infusion. Infusion reactions typically occurred within 30 to 120 minutes of beginning the first infusion and resolved with slowing or interruption of the Rituxan infusion and with supportive care (diphenhydramine, acetaminophen, and intravenous saline). The incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion. [*See Boxed Warning, Warnings and Precautions (5.1).*]

Infections

Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of patients with NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial 19%, viral 10%, unknown 6%, and fungal 1%). [*See Warnings and Precautions (5.4), (5.5), (5.6).*]

In randomized, controlled studies where Rituxan was administered following chemotherapy for the treatment of follicular or low-grade NHL, the rate of infection was higher among patients who received Rituxan. In diffuse large B-cell lymphoma patients, viral infections occurred more frequently in those who received Rituxan.

Cytopenias and hypogammaglobulinemia

In patients with NHL receiving rituximab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1–588 days) and of neutropenia was 13 days (range, 2–116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituxan therapy occurred during the single-arm studies.

In studies of monotherapy, Rituxan-induced B-cell depletion occurred in 70% to 80% of patients with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients.

Single-Agent Rituxan

Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a single agent [*see Clinical Studies (14.1)*]. Most patients received Rituxan 375 mg/m^2 weekly for 4 doses.

Table 1

Incidence of Adverse Reactions in ≥ 5% of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL, Receiving Single-agent Rituxan (N = 356)[a,b]

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Reactions	99	57
Body as a Whole	86	10
Fever	53	1
Chills	33	3
Infection	31	4
Asthenia	26	1
Headache	19	1
Abdominal Pain	14	1
Pain	12	1
Back Pain	10	1
Throat Irritation	9	0
Flushing	5	0
Heme and Lymphatic System	67	48
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
Skin and Appendages	44	2
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1
Respiratory System	38	4
Increased Cough	13	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
Metabolic and Nutritional Disorders	38	3
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0

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Table 1 (cont'd)

Incidence of Adverse Reactions in ≥ 5% of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL, Receiving Single-agent Rituxan (N = 356)[a,b]

	All Grades (%)	Grade 3 and 4 (%)
Digestive System	37	2
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
Nervous System	32	1
Dizziness	10	1
Anxiety	5	1
Musculoskeletal System	26	3
Myalgia	10	1
Arthralgia	10	1
Cardiovascular System	25	3
Hypotension	10	1
Hypertension	6	1

[a] Adverse reactions observed up to 12 months following Rituxan.
[b] Adverse reactions graded for severity by NCI-CTC criteria.

In these single-arm Rituxan studies, bronchiolitis obliterans occurred during and up to 6 months after Rituxan infusion.

Rituxan in Combination with Chemotherapy

Adverse reactions information below is based on 1250 patients who received Rituxan in combination with chemotherapy or following chemotherapy.

Rituxan in Combination with Chemotherapy for Low-Grade NHL

In Study 4, patients in the R-CVP arm experienced a higher incidence of infusional toxicity and neutropenia compared to patients in the CVP arm. The following adverse reactions occurred more frequently (≥ 5%) in patients receiving R-CVP compared to CVP alone: rash (17% vs. 5%), cough (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8% vs. 3%), and chest tightness (7% vs. 1%). [*See Clinical Studies (14.2).*]

In Study 5, the following adverse reactions were reported more frequently (≥ 5%) in patients receiving Rituxan following CVP compared to patients who received no further therapy: fatigue (39% vs. 14%), anemia (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections (19% vs. 9%), pulmonary toxicity (18% vs. 10%), hepato-biliary toxicity (17% vs. 7%), rash and/or pruritus (17% vs. 5%), arthralgia (12% vs. 3%), and weight gain (11% vs. 4%). Neutropenia was the only Grade 3 or 4 adverse reaction that occurred more frequently

(≥ 2%) in the Rituxan arm compared with those who received no further therapy (4% vs. 1%). [*See Clinical Studies (14.3).*]

Rituxan in Combination with Chemotherapy for DLBCL

In Studies 6 and 7, *[see Clinical Studies (14.4)]*, the following adverse reactions, regardless of severity, were reported more frequently (≥ 5%) in patients age ≥ 60 years receiving R-CHOP as compared to CHOP alone: pyrexia (56% vs. 46%), lung disorder (31% vs. 24%), cardiac disorder (29% vs. 21%), and chills (13% vs. 4%). Detailed safety data collection in these studies was primarily limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

In Study 7, a review of cardiac toxicity determined that supraventricular arrhythmias or tachycardia accounted for most of the difference in cardiac disorders (4.5% for R-CHOP vs. 1.0% for CHOP).

The following Grade 3 or 4 adverse reactions occurred more frequently among patients in the R-CHOP arm compared with those in the CHOP arm: thrombocytopenia (9% vs. 7%) and lung disorder (6% vs. 3%). Other Grade 3 or 4 adverse reactions occurring more frequently among patients receiving R-CHOP were viral infection (Study 7), neutropenia (Studies 7 and 8), and anemia (Study 8).

6.2 Clinical Trials Experience Rheumatoid Arthritis

The types of adverse reactions observed in patients with RA were similar to those seen in patients with non-Hodgkin's lymphoma [*see Warnings and Precautions (5), Adverse Reactions (6.1)*]. Specific safety considerations in this indication are discussed below.

Where specific percentages are noted, these data are based on 938 patients treated in Phase 2 and 3 studies of Rituxan (2 × 1000 mg) or placebo administered in combination with methotrexate.

Table 2

Incidence of All Adverse Reactions* Occurring in ≥ 2% and at Least 1% Greater than Placebo Among Rheumatoid Arthritis Patients in Clinical Studies Up to Week 24 (Pooled)

Preferred Term	Placebo + MTX N = 398 n (%)	Rituxan + MTX N = 540 n (%)
Hypertension	21 (5)	43 (8)
Nausea	19 (5)	41 (8)
Upper Respiratory Tract Infection	23 (6)	37 (7)
Arthralgia	14 (4)	31 (6)
Pyrexia	8 (2)	27 (5)
Pruritus	5 (1)	26 (5)
Chills	9 (2)	16 (3)
Dyspepsia	3 (< 1)	16 (3)
Rhinitis	6 (2)	14 (3)
Paresthesia	3 (< 1)	12 (2)
Urticaria	3 (< 1)	12 (2)
Abdominal Pain Upper	4 (1)	11 (2)
Throat Irritation	0 (0)	11 (2)
Anxiety	5 (1)	9 (2)
Migraine	2 (< 1)	9 (2)
Asthenia	1 (< 1)	9 (2)

*Coded using MedDRA.

Infusion Reactions

In Rituxan RA placebo-controlled studies, 32% of Rituxan-treated patients experienced an adverse reaction during or within 24 hours following their first infusion, compared to 23% of placebo-treated patients receiving their first infusion. The incidence of adverse reactions during the 24-hour period following the second infusion, Rituxan or placebo, decreased to 11% and 13%, respectively. Acute infusion reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash, angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated hypotension or hypertension) were experienced by 27% of Rituxan-treated patients following their first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion. The incidence of these acute infusion reactions following the second infusion of Rituxan or placebo decreased to 9% and 11%, respectively. Serious acute infusion reactions were experienced by < 1% of patients in either treatment group. Acute infusion reactions required dose modification (stopping, slowing, or interruption of the infusion) in 10% and 2% of patients receiving rituximab or placebo, respectively, after the first course. The proportion of patients experiencing acute infusion reactions decreased with subsequent courses of Rituxan. The administration of intravenous glucocorticoids prior to Rituxan infusions reduced the incidence and severity of such reactions, however, there was no clear benefit from the

administration of oral glucocorticoids for the prevention of acute infusion reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to Rituxan infusions.

Infections

In RA clinical studies, 39% of patients in the Rituxan group experienced an infection of any type compared to 34% of patients in the placebo group. The most common infections were nasopharyngitis, upper respiratory tract infections, urinary tract infections, bronchitis, and sinusitis.

The incidence of serious infections was 2% in the Rituxan-treated patients and 1% in the placebo group. One fatal infection (bronchopneumonia) occurred with rituximab monotherapy during the 24-week, placebo-controlled period in one of the Phase 2 RA studies. In 107 Rituxan-treated RA patients with active disease, subsequent treatment with a TNF inhibitor was associated with a higher rate of serious infections. Six serious infections were observed in 100.8 patient years (0.06 per patient year) prior to exposure and 9 were observed in 97.8 patient years (0.09 per patient year) after exposure.

Cardiac Adverse Reactions

The incidence of serious cardiovascular events in the double-blind part of the RA clinical trials was 1.7% and 1.3% in Rituxan and placebo treatment groups, respectively. Three cardiovascular deaths occurred during the double-blind period of the RA studies including all rituximab regimens (3/769 = 0.4%) as compared to none in the placebo treatment group (0/389).

Since patients with RA are at increased risk for cardiovascular events compared with the general population, patients with RA should be monitored throughout the infusion and Rituxan should be discontinued in the event of a serious or life-threatening cardiac event.

Hypophosphatemia and hyperuricemia

In the 24-week, double-blind RA clinical trial program, newly-occurring hypophosphatemia (<2.0 mg/dl) was observed in 12% (67/540) of patients on Rituxan versus 10% (39/398) of patients on placebo. Hypophosphatemia was more common in patients who received corticosteroids. Newly-occurring hyperuricemia (>10 mg/dl) was observed in 1.5% (8/540) of patients on Rituxan versus 0.3% (1/398) of patients on placebo.

At any time after treatment with up to seven courses of Rituxan, at least one episode of newly-occurring hypophosphatemia was observed in 23% (245/1048) of patients and newly-occurring hyperuricemia was observed in 3% (32/1048) of patients.

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody (including neutralizing antibody)

positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Rituxan with the incidence of antibodies to other products may be misleading.

Using an ELISA assay, anti-human anti-chimeric antibody (HACA) was detected in 4 of 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent Rituxan. Three of the four patients had an objective clinical response.

A total of 118/1053 patients (11%) with RA tested positive for HACA at any time after treatment with Rituxan. Limited data are available on the safety or efficacy of Rituxan retreatment in patients who develop HACA. Of the 8 patients who experienced serious acute infusion reactions, 2 were subsequently found to be HACA-positive. Approximately 12% (14/118) of patients who were HACA-positive had a subsequent infusion reaction of any severity. The clinical relevance of HACA formation in rituximab-treated patients is unclear.

6.4 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Rituxan in hematologic malignancies. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to Rituxan.

- Hematologic: prolonged pancytopenia, marrow hypoplasia, and late-onset neutropenia, hyperviscosity syndrome in Waldenstrom's macroglobulinemia.
- Cardiac: fatal cardiac failure.
- Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- Infection: viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of Grade 3 and 4 infections in patients with previously treated lymphoma without known HIV infection.
- Neoplasia: disease progression of Kaposi's sarcoma.
- Skin: severe mucocutaneous reactions.
- Gastrointestinal: bowel obstruction and perforation.
- Pulmonary: fatal bronchiolitis obliterans and pneumonitis (including interstitial pneumonitis).

7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with Rituxan. In clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of rituximab.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category C: There are no adequate and well-controlled studies of rituximab in pregnant women. Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed in-utero.

Non-Hodgkin's lymphoma and moderate-severe rheumatoid arthritis are serious conditions that require treatment. Rituximab should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Reproduction studies in cynomolgus monkeys at maternal exposures similar to human therapeutic exposures showed no evidence of teratogenic effects. However, B-cell lymphoid tissue was reduced in the offspring of treated dams. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months of birth.

8.3 Nursing Mothers

It is not known whether Rituxan is secreted into human milk. However, Rituxan is secreted in the milk of lactating cynomolgus monkeys, and IgG is excreted in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. The unknown risks to the infant from oral ingestion of Rituxan should be weighed against the known benefits of breastfeeding.

8.4 Pediatric Use

The safety and effectiveness of Rituxan in pediatric patients have not been established.

8.5 Geriatric Use

Diffuse Large B-Cell NHL

Among patients with DLBCL evaluated in three randomized, active-controlled trials, 927 patients received Rituxan in combination with chemotherapy. Of these, 396 (43%) were age 65 or greater and 123 (13%) were age 75 or greater. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse reactions, mostly supraventricular arrhythmias, occurred more frequently among elderly patients. Serious pulmonary adverse reactions were also more common among the elderly, including pneumonia and pneumonitis.

Low-Grade or Follicular Non-Hodgkin's Lymphoma

Clinical studies of Rituxan in low-grade or follicular, CD20-positive, B-cell NHL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

Rheumatoid Arthritis

Among the 517 patients in the Phase 3 RA study, 16% were 65–75 years old and 2% were 75 years old and older. Response rates and adverse reactions were similar in the older (age ≥ 65 years) and younger (age < 65 years) patients.

10 OVERDOSAGE

There has been no experience with overdosage in human clinical trials. Single doses of up to 500 mg/m^2 have been given in dose-escalation clinical trials.

11 DESCRIPTION

Rituxan® (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG_1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Water for Injection. The pH is 6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes. The antigen is expressed on > 90% of B-cell non-Hodgkin's lymphomas (NHL), but the antigen is not found on hematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissues. CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. CD20 is not shed from the cell surface and does not internalize upon antibody binding. Free CD20 antigen is not found in the circulation.

B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process,

including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or pro-inflammatory cytokine production.

Mechanism of Action: The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.

Normal Tissue Cross-reactivity: Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

12.2 Pharmacodynamics

Administration of Rituxan resulted in a rapid and sustained depletion of circulating and tissue-based B cells. Among 166 patients in Study 1, circulating CD19-positive B cells were depleted within the first three weeks with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients. B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by 12 months following completion of treatment.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following rituximab administration; 14% of patients had IgM and/or IgG serum levels below the normal range.

In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with all patients demonstrating near complete depletion within 2 weeks after receiving the first dose of Rituxan. The majority of patients showed peripheral B-cell depletion for at least 6 months, followed by subsequent gradual recovery after that timepoint. A small proportion of patients (4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of treatment.

In RA studies, total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the greatest change observed in IgM. However, mean immunoglobulin levels remained within normal levels over the 24-week period. Small proportions of patients experienced decreases in IgM (7%), IgG (2%), and IgA (1%) levels below the lower limit of normal. The clinical consequences of decreases in immunoglobulin levels in RA patients treated with Rituxan are unclear.

Treatment with rituximab in patients with RA was associated with reduction of certain biologic markers of inflammation such as interleukin-6 (IL-6), C-reactive protein (CRP), serum amyloid protein (SAA), S100 A8/S100 A9 heterodimer complex (S100 A8/9), anti-citrullinated peptide (anti-CCP), and RF.

12.3 Pharmacokinetics

Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m^2 rituximab weekly by IV infusion for 4 doses. The mean C_{max} increased with each successive infusion and was 486 mcg/mL (range, 78–997 mcg/mL) following the fourth infusion. Peak and trough serum levels of rituximab were inversely correlated with pretreatment circulating CD19-positive B cells and tumor burden. Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.

The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Based on a population pharmacokinetic analysis of data from 298 NHL patients who received rituximab once weekly or once every three weeks, the estimated median terminal elimination half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the pharmacokinetics of rituximab.

Following administration of 2 doses of rituximab in patients with rheumatoid arthritis, the mean C_{max} values were 183 mcg/mL (CV = 24%) for the 2 × 500 mg dose and 370 mcg/mL (CV = 25%) for the 2 × 1000 mg dose, respectively. Following 2 × 1000 mg rituximab dose, mean volume of distribution at steady state was 4.3L (CV = 28%). Mean systemic serum clearance of rituximab was 0.01L/h (CV = 38%), and mean terminal elimination half-life after the second dose was 19 days (CV = 32%).

Female patients with RA (n = 86) had a 37% lower clearance of rituximab than male patients with RA (n = 25). The gender difference in rituximab clearance does not necessitate any dose adjustment because safety and efficacy of rituximab do not appear to be influenced by gender.

The pharmacokinetics of rituximab have not been studied in children and adolescents. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of rituximab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of Rituxan or to determine potential effects on fertility in males or females.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received rituximab via

the intravenous route during early gestation (organogenesis period; post-coitum days 20 through 50). Rituximab was administered as loading doses on post-coitum (PC) days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells.

A subsequent pre- and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from PC Day 20 through postpartum Day 78, PC Day 76 through PC Day 134, and from PC day 132 through delivery and postpartum Day 28. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

The safety and effectiveness of Rituxan in relapsed, refractory CD20+ NHL were demonstrated in 3 single-arm studies enrolling 296 patients.

Study 1

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory, low-grade or follicular, B-cell NHL who received 375 mg/m^2 of Rituxan given as an intravenous infusion weekly for 4 doses. Patients with tumor masses > 10 cm or with > 5000 lymphocytes/μL in the peripheral blood were excluded from the study.

Results are summarized in Table 3. The median time to onset of response was 50 days. Disease-related signs and symptoms (including B-symptoms) resolved in 64% (25/39) of those patients with such symptoms at study entry.

Study 2

In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL received 375 mg/m^2 of Rituxan weekly for 8 doses. Results are summarized in Table 3.

Study 3

In a multicenter, single-arm study, 60 patients received 375 mg/m^2 of Rituxan weekly for 4 doses. All patients had relapsed or refractory,

low-grade or follicular, B-cell NHL and had achieved an objective clinical response to Rituxan administered 3.8–35.6 months (median 14.5 months) prior to retreatment with Rituxan. Of these 60 patients, 5 received more than one additional course of Rituxan. Results are summarized in Table 3.

Bulky Disease

In pooled data from studies 1 and 3, 39 patients with bulky (single lesion > 10 cm in diameter) and relapsed or refractory, low-grade NHL received Rituxan 375 mg/m^2 weekly for 4 doses. Results are summarized in Table 3.

Table 3
Summary of Rituxan Efficacy Data by Schedule and Clinical Setting

	Study 1 Weekly × 4 N = 166	Study 2 Weekly × 8 N = 37	Study 1 and Study 3 Bulky disease, Weekly × 4 N = 39[a]	Study 3 Retreatment, Weekly × 4 N = 60
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration of Response[b, c, d] (Months) [Range]	11.2 [1.9 to 42.1+]	13.4 [2.5 to 36.5+]	6.9 [2.8 to 25.0+]	15.0 [3.0 to 25.1+]

[a] Six of these patients are included in the first column. Thus, data from 296 intent-to-treat patients are provided in this table.
[b] Kaplan-Meier projected with observed range.
[c] "+" indicates an ongoing response.
[d] Duration of response: interval from the onset of response to disease progression.

14.2 Previously Untreated, Follicular, CD20-Positive, B-Cell NHL

Study 4

A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with Rituxan 375 mg/m^2 on Day 1 of each cycle (R-CVP) in an open-label, multicenter study. The main outcome measure of the study was progression-free survival (PFS) defined as the time from randomization to the first of progression, relapse, or death.

Twenty-six percent of the study population was > 60 years of age, 99% had Stage III or IV disease, and 50% had an International Prognostic Index (IPI) score ≥ 2. The results for PFS as determined by a blinded, independent assessment of progression are presented in Table 4. The point estimates may be influenced by the presence of informative censoring. The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

Table 4
Efficacy Results in Study 4

	Study Arm	
	R-CVP N=162	CVP N=160
Median PFS (years)[a]	2.4	1.4
Hazard ratio (95% CI)[b]	0.44 (0.29, 0.65)	

[a] $p < 0.0001$, two-sided stratified log-rank test.
[b] Estimates of Cox regression stratified by center.

14.3 Non-Progressing Low-Grade, CD20-Positive, B-Cell NHL Following First-Line CVP Chemotherapy

Study 5

A total of 322 patients with previously untreated low-grade, B-cell NHL who did not progress after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter, randomized trial. Patients were randomized (1:1) to receive Rituxan, 375 mg/m^2 intravenous infusion, once weekly for 4 doses every 6 months for up to 16 doses or no further therapeutic intervention. The main outcome measure of the study was progression-free survival defined as the time from randomization to progression, relapse, or death. Thirty-seven percent of the study population was > 60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score ≥ 2.

There was a reduction in the risk of progression, relapse, or death (hazard ratio estimate in the range of 0.36 to 0.49) for patients randomized to Rituxan as compared to those who received no additional treatment.

14.4 Diffuse Large B-Cell NHL (DLBCL)

The safety and effectiveness of Rituxan were evaluated in three randomized, active-controlled, open-label, multicenter studies with a collective enrollment of 1854 patients. Patients with previously untreated diffuse large B-cell NHL received Rituxan in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

Study 6

A total of 632 patients age ≥ 60 years with DLBCL (including primary mediastinal B-cell lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses of Rituxan 375 mg/m^2 on Days -7 and -3 (prior to Cycle 1) and 48–72 hours prior to Cycles 3 and 5. Patients who received 8 cycles of CHOP also received Rituxan prior to cycle 7. The main outcome measure of the study was progression-free survival, defined as the time from randomization to the first of progression, relapse, or death. Responding patients underwent a second randomization to receive Rituxan or no further therapy.

Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had Stage III–IV disease, 56% had IPI scores ≥ 2, 86%

had ECOG performance status of < 2, 57% had elevated LDH levels, and 30% had two or more extranodal disease sites involved. Efficacy results are presented in Table 5. These results reflect a statistical approach which allows for an evaluation of Rituxan administered in the induction setting that excludes any potential impact of Rituxan given after the second randomization.

Analysis of results after the second randomization in Study 6 demonstrates that for patients randomized to R-CHOP, additional Rituxan exposure beyond induction was not associated with further improvements in progression-free survival or overall survival.

Study 7

A total of 399 patients with DLBCL, age ≥ 60 years, were randomized in a 1:1 ratio to receive CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP induction; patients in the R-CHOP arm received Rituxan 375 mg/m^2 on Day 1 of each cycle. The main outcome measure of the study was event-free survival, defined as the time from randomization to relapse, progression, change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV disease, 60% of patients had an age-adjusted IPI ≥ 2, 80% had ECOG performance status scores < 2, 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites. Efficacy results are presented in Table 5.

Study 8

A total of 823 patients with DLBCL, aged 18−60 years, were randomized in a 1:1 ratio to receive an anthracycline-containing chemotherapy regimen alone or in combination with Rituxan. The main outcome measure of the study was time to treatment failure, defined as time from randomization to the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among all enrolled patients, 28% had Stage III−IV disease, 100% had IPI scores of ≤ 1, 99% had ECOG performance status of < 2, 29% had elevated LDH levels, 49% had bulky disease, and 34% had extranodal involvement. Efficacy results are presented in Table 5.

Table 5
Efficacy Results in Studies 6, 7, and 8

	Study 6 (n = 632)		Study 7 (n = 399)		Study 8 (n = 823)	
	R-CHOP	CHOP	R-CHOP	CHOP	R-Chemo	Chemo
Main outcome	Progression-free survival (years)		Event-free survival (years)		Time to treatment failure (years)	
Median of main outcome measure	3.1	1.6	2.9	1.1	NE[b]	NE[b]
Hazard ratio[d]	0.69[a]		0.60[a]		0.45[a]	
Overall survival at 2 years[c]	74%	63%	69%	58%	95%	86%
Hazard ratio[d]	0.72[a]		0.68[a]		0.40[a]	

[a] Significant at $p < 0.05$, 2-sided.
[b] NE = Not reliably estimable.
[c] Kaplan-Meier estimates.
[d] R-CHOP vs. CHOP.

In Study 7, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.

14.5 Rheumatoid Arthritis (RA)

The efficacy and safety of Rituxan were evaluated in 517 patients with active disease who were receiving methotrexate and had a prior inadequate response to at least one TNF inhibitor. Patients were ≥ 18 years, diagnosed with RA according to American College of Rheumatology (ACR) criteria, and had at least 8 swollen and 8 tender joints. Patients received 2 doses of either Rituxan 1000 mg or placebo as an intravenous infusion on days 1 and 15, in combination with continued methotrexate 10–25 mg weekly.

Efficacy was assessed at 24 weeks. Glucocorticoids were given intravenously prior to each Rituxan infusion and orally on a tapering schedule from baseline through Day 16.

The proportions of Rituxan (1000 mg) treated patients achieving ACR 20, 50, and 70 responses in this study is shown in Table 6.

Table 6

ACR Responses at Week 24 in
Placebo-Controlled Study (Percent of Patients)
(Modified Intent-to-Treat Population)

Response	Placebo + MTX n = 201	Rituxan + MTX n = 298
ACR 20	18%	51%
		p < 0.0001
ACR 50	5%	27%
		p < 0.0001
ACR 70	1%	12%
		p < 0.0001

Improvement was also noted for all components of ACR response following treatment with Rituxan, as shown in Table 7.

Table 7

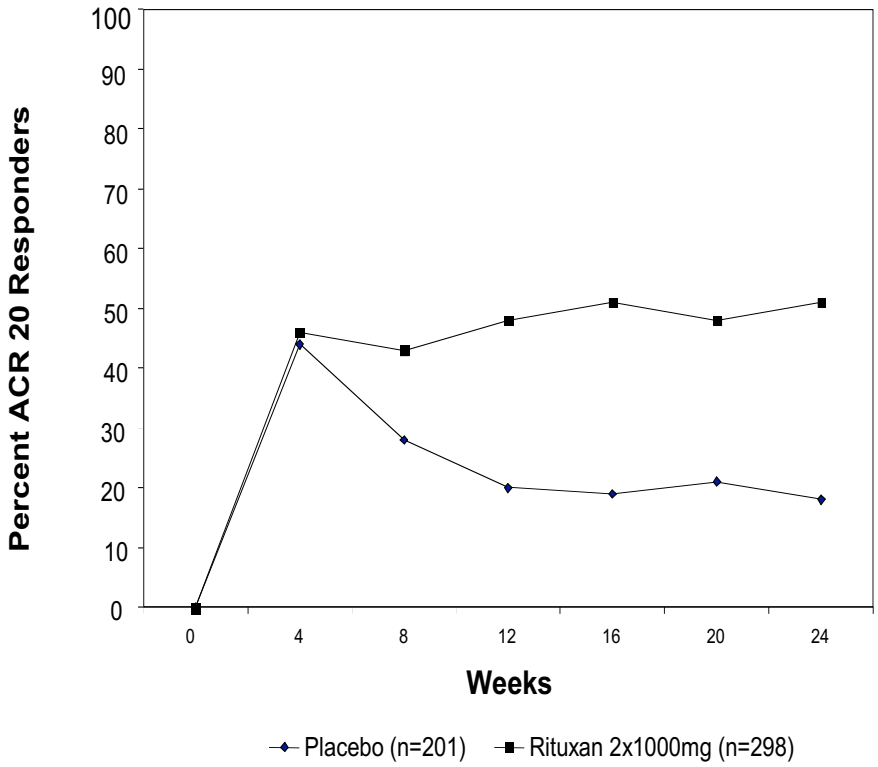
Components of ACR Response
(Modified Intent-to-Treat Population)

Parameter (median)	Placebo + MTX (n = 201)		Rituxan + MTX (n = 298)	
	Baseline	Wk 24	Baseline	Wk 24
Tender Joint Count	31.0	27.0	33.0	13.0*
Swollen Joint Count	20.0	19.0	21.0	9.5*
Physician Global Assessment [a]	71.0	69.0	71.0	36.0*
Patient Global Assessment [a]	73.0	68.0	71.0	41.0*
Pain [a]	68.0	68.0	67.0	38.5*
Disability Index (HAQ) [b]	2.0	1.9	1.9	1.5*
CRP (mg/dL)	2.4	2.5	2.6	0.9*

[a] Visual Analogue Scale: 0 = best, 100 = worst.
[b] Disability Index of the Health Assessment Questionnaire: 0 = best, 3 = worst.
* p < 0.001, Rituxan + MTX vs. Placebo + MTX.

The time course of ACR 20 response for this study is shown in Figure 1. Although both treatment groups received a brief course of intravenous and oral glucocorticoids, resulting in similar benefits at week 4, higher ACR 20 responses were observed for the Rituxan group by week 8 and were maintained through week 24 after a single course of treatment (2 infusions) with Rituxan. Similar patterns were demonstrated for ACR 50 and 70 responses.

Figure 1
ACR 20 Responses Over 24 Weeks



While the efficacy of Rituxan was supported by two well-controlled trials in RA patients who had inadequate responses to non-biologic DMARDs, but who had not failed TNF antagonist therapy, a favorable risk benefit relationship has not been established in this population [*see Warnings and Precautions (5.13)*].

Radiographic Response

Structural joint damage was assessed radiographically and expressed as changes in Sharp-Genant Total Score and its components, joint space narrowing score and erosion score. The results are shown in Table 8. Rituxan plus MTX slowed the progression of structural damage compared to placebo plus MTX at 56 weeks.

Table 8
Mean Radiographic Change From Baseline to 56 Weeks

Parameter	Placebo + MTX (n=184) Mean Change	Rituxan + MTX (n=273) Mean Change	Treatment Difference (Placebo - Rituxan)	95% CI for the Treatment Difference
Sharp-Genant Total Score	2.31	1.00	1.31	(0.48, 2.14)
Total Joint Space Narrowing Score	0.99	0.41	0.58	(0.18, 0.98)
Total Erosion Score	1.32	0.59	0.73	(0.22, 1.24)

16 HOW SUPPLIED/STORAGE AND HANDLING

Rituxan vials [100 mg (NDC 50242-051-21) and 500 mg (NDC 50242-053-06)] are stable at 2°C–8°C (36°F–46°F). Do not use beyond expiration date stamped on carton. Rituxan vials should be protected from direct sunlight. Do not freeze or shake.

Rituxan solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours. Rituxan solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since Rituxan solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between Rituxan and polyvinylchloride or polyethylene bags have been observed.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.2).

17.1 General Counseling Information

Patients should be provided the Rituxan Medication Guide and provided an opportunity to read prior to each treatment session. Because caution should be exercised in administering Rituxan to patients with active infections, it is important that the patient's overall health be assessed at each visit and any questions resulting from the patient's reading of the Medication Guide be discussed.

Rituxan is detectable in serum for up to six months following completion of therapy. Individuals of childbearing potential should use effective contraception during treatment and for 12 months after Rituxan therapy.

17.2 Medication Guide

MEDICATION GUIDE
RITUXAN® (ri-tuk´-san)
(rituximab)

Read the Medication Guide given to you before you start Rituxan and before each Rituxan infusion. The information may have changed. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment. Talk with your doctor if you have any questions about your treatment with Rituxan.

What is the most important information I should know about Rituxan?

Rituxan can cause serious side effects including:

- **Progressive Multifocal Leukoencephalopathy (PML)**
  - PML is a rare brain infection. PML usually causes death or severe disability.
  - Call your doctor right away if you notice any new or worsening medical problems, such as a new or sudden change in thinking, walking, strength, vision, or other problems that have lasted over several days.
  - PML usually happens in patients with weakened immune systems.
  - PML can occur during treatment with Rituxan or after treatment has finished.
  - There is no known treatment, prevention, or cure for PML.
- **Infusion reactions**. Tell your doctor or get medical treatment right away if you get hives, swelling, dizziness, blurred vision, drowsiness, headache, cough, wheezing, or have trouble breathing while receiving or after receiving Rituxan.
- **Tumor Lysis Syndrome (TLS)**. TLS is caused by the fast breakdown of certain types of cancer cells. TLS can cause kidney failure and the need for dialysis treatment. Patients receiving Rituxan for non-Hodgkin's lymphoma (NHL) may get TLS. Your doctor will check you for TLS.
- **Severe skin reactions**. Tell your doctor or get medical treatment right away if you get any of these symptoms: painful sores on your skin or in your mouth, ulcers, blisters, or peeling skin while receiving or after receiving Rituxan.

See "**What are possible side effects with Rituxan?"** for other serious side effects.

What is Rituxan?

Rituxan is a prescription medicine used in adults:

- alone or with other anti-cancer medicines to treat certain types of NHL.
- with another medicine called methotrexate to reduce the signs and symptoms of Rheumatoid Arthritis (RA) after at least one other medicine called a tumor necrosis factor (TNF) inhibitor has been used and did not work well.

Rituxan has not been studied in children.

What should I tell my doctor before treatment with Rituxan?

Tell your doctor about all of your medical conditions, including if you:

- had a severe infusion reaction to Rituxan in the past.
- have an infection or have an infection that will not go away or that keeps coming back.
- have or had hepatitis (liver) infection. See "**What are the possible side effects of Rituxan**?" If so, your doctor should check you closely for signs of hepatitis infection during treatment with Rituxan and for several months after treatment ends.
- are scheduled to receive any vaccinations. You should not receive live vaccines after you receive Rituxan.
- have heart or lung problems.
- are pregnant or planning to become pregnant. It is not known if Rituxan can harm your unborn baby.
- are breastfeeding. It is not known if Rituxan passes into human breast milk. You should not breastfeed while being treated with Rituxan and after finishing treatment, until blood tests show that there is no Rituxan in your blood.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, or herbal supplements. If you have RA, especially tell your doctor if you take or have taken another medicine called a TNF inhibitor or a DMARD (disease modifying anti-rheumatic drug).

How do I receive Rituxan?

- Rituxan is given through a needle placed in a vein (IV or intravenous infusion), in your arm. Talk to your doctor about how you will receive Rituxan.
- Your doctor may prescribe medicines before each infusion of Rituxan to reduce side effects of infusions (such as fever and chills).
- Your doctor should do regular blood tests to check for side effects to Rituxan.

Before each Rituxan treatment, your doctor or nurse will ask you questions about your general health to make sure that Rituxan is still right for you. Tell your doctor or nurse about any new symptoms, and symptoms that get worse over a few days or that will not go away.

What are the possible side effects of Rituxan?

The **"What is the most important information I should know about Rituxan?"** section lists certain serious and life-threatening side effects with Rituxan. Rituxan can cause other serious and life-threatening side effects including:

- **Hepatitis B virus reactivation.** Tell your doctor if you had hepatitis B virus or are a carrier of hepatitis B virus. Receiving Rituxan could cause the hepatitis B virus to become an active infection again. This may cause serious liver problems and death. People with active liver disease due to hepatitis B should stop receiving Rituxan.
- **Heart problems.** Tell your doctor about any heart problems you have including chest pain (angina) and irregular heart beats. Rituxan can cause chest pain and irregular heart beats which may require treatment.
- **Infections.** Rituxan can increase your chances for getting infections. Call your doctor right away if you have a cough that will not go away, fever, chills, congestion, or any flu-like symptoms while receiving Rituxan. These symptoms may be signs of a serious infection.
- **Stomach and bowel problems.** Serious stomach and bowel problems have been seen when Rituxan has been used with anti-cancer medicines in some patients with non-Hodgkin's lymphoma. Call your doctor right away if you have any stomach area pain during treatment with Rituxan.

Common side effects during Rituxan infusions include:

- fever
- chills and shakes
- itching
- cough
- throat irritation or tightness
- headache
- nausea
- hives
- sneezing

Other side effects with Rituxan include:

- aching joints
- upper respiratory tract infection
- decreased blood cell counts
- lung problems

Tell your doctor about any side effect that bothers you or that does not go away. These are not all of the possible side effects with Rituxan. Ask your doctor for more information.

General Information about Rituxan

This Medication Guide provides a summary of the most important information about Rituxan. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information or have any questions, talk with your doctor. You can ask your doctor for information about Rituxan that is written for healthcare professionals. You can also visit www.Rituxan.com or call 1-877-474-8892.

What are the ingredients in Rituxan?

Active ingredient: rituximab

Inactive ingredients: sodium chloride, sodium citrate dihydrate, polysorbate 80, and water for injection.

Jointly Marketed by: Biogen Idec Inc. and Genentech USA, Inc.

Manufactured by:

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Revised 09/2008 (4835505)

This Medication Guide has been approved by the U.S. Food and Drug Administration.

14.3 Methotrexate United States Prescribing Information

Reparin LABORATORIES

METHOTREXATE INJECTION, USP
METHOTREXATE FOR INJECTION, USP

Rx ONLY

WARNINGS

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY.

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL):

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.

DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS.

PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See **PRECAUTIONS.**)

PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.

THE USE OF METHOTREXATE HIGH DOSE REGIMENS RECOMMENDED FOR OSTEOSARCOMA REQUIRES METICULOUS CARE. (See **DOSAGE AND ADMINISTRATION.**) HIGH DOSE REGIMENS FOR OTHER NEOPLASTIC DISEASES ARE INVESTIGATIONAL AND A THERAPEUTIC ADVANTAGE HAS NOT BEEN ESTABLISHED.

METHOTREXATE FORMULATIONS AND DILUENTS CONTAINING PRESERVATIVES MUST NOT BE USED FOR INTRATHECAL OR HIGH DOSE METHOTREXATE THERAPY.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate (See **CONTRAINDICATIONS**).

2. Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.

3. Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See **PRECAUTIONS, Drug Interactions.**)

4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population. (See **PRECAUTIONS, Organ System Toxicity**, *Hepatic*.)

5. Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.

6. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.

8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See **PRECAUTIONS, Organ System Toxicity**, *Skin*.)

10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.

11. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

DESCRIPTION

Methotrexate is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis. Chemically methotrexate is L-(+)-*N*-[*p*-[[(2,4-Diamino-6-pteridinyl)methyl]methylamino]-benzoyl]glutamic acid. The structural formula is:

$C_{20}H_{22}N_8O_5$ M.W.=454.44

Methotrexate for injection and Methotrexate injection (Preservative Free) products are sterile and non-pyrogenic and may be given by the intramuscular, intravenous, intra-arterial or intrathecal route. (See **DOSAGE AND ADMINISTRATION**.)

Methotrexate Injection, USP, isotonic liquid, preservative free, for single use only, is available in 25 mg/mL, 2 mL (50 mg), 4 mL (100 mg), 8 mL (200 mg), and 10 mL (250 mg) vials.

Each 25 mg/mL, 2 mL, 4 mL, 8 mL, and 10 mL vial contains methotrexate sodium equivalent to 50 mg, 100 mg, 200 mg, and 250 mg methotrexate respectively, and the following inactive ingredients: sodium chloride 0.490% *w/v* and water for injection qs ad 100% *v*. Sodium hydroxide and, if necessary, hydrochloric acid are added to adjust the pH to approximately 8.5. The 2 mL, 4 mL, 8 mL, and 10 mL solutions contain approximately 0.43 mEq, 0.86 mEq, 1.72 mEq, and 2.15 mEq of sodium per vial, respectively, and are isotonic solutions.

Methotrexate for Injection, USP, lyophilized, preservative free, for single use only, is available in 1 gram vials.

Each 1 gram vial of lyophilized powder contains methotrexate sodium equivalent to 1 gram methotrexate. Contains no preservative. Sodium hydroxide and, if necessary, hydrochloric acid are added during manufacture to adjust the pH. The 1 gram vial contains approximately 7 mEq sodium.

CLINICAL PHARMACOLOGY

Methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa and cells of the urinary bladder are in general more sensitive to this effect of methotrexate. When cellular proliferation in malignant tissues is greater than in most normal tissues, methotrexate may impair malignant growth without irreversible damage to normal tissues.

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function. Two reports describe *in vitro* methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes in animal polyarthritis partial correction by methotrexate of splean cell hyperresponsiveness and suppressed IL 2 production. Other laboratories, however, have been unable to demonstrate similar effects. Clarification of methotrexate's effect on immune activity and its relation to rheumatoid immunopathogenesis await further studies.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as 3 to 6 weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness), there is no evidence that it induces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiologic changes which result in impaired joint use, functional disability, and deformity.

Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (3 to 6 months). Limited data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

Methotrexate in high doses, followed by leucovorin rescue, is used as a part of the treatment of patients with non-metastatic osteosarcoma. The original rationale for high dose methotrexate therapy was based on the concept of selective rescue of normal tissues by leucovorin. More recent evidence suggests that high dose methotrexate may also overcome methotrexate resistance caused by impaired active transport, decreased affinity of dihydrofolic acid reductase for methotrexate, increased levels of dihydrofolic acid reductase resulting from gene amplification, or decreased polyglutamation of methotrexate. The actual mechanism of action is unknown.

In a 6-month double-blind, placebo-controlled trial of 127 pediatric patients with juvenile rheumatoid arthritis (JRA) (mean age, 10.1 years; age range, 2.5 to 18 years; mean duration of disease, 5.1 years) on background nonsteroidal anti-inflammatory drugs (NSAIDs) and/or prednisone, methotrexate given weekly at an oral dose of 10 mg/m² provided significant clinical improvement compared to placebo as measured by either the physician's global assessment, or by a patient composite (25% reduction in the articular-severity score plus improvement in parent and physician global assessments of disease activity). Over two-thirds of the patients in this trial had polyarticular-course JRA, and the numerically greatest response was seen in this subgroup treated with 10 mg/m²/wk methotrexate. The overwhelming majority of the remaining patients had systemic-course JRA. All patients were unresponsive to NSAIDs; approximately one-third were using low dose corticosteroids. Weekly methotrexate at a dose of 5 mg/m² was not significantly more effective than placebo in this trial.

Two Pediatric Oncology Group studies (one randomized and one non-randomized) demonstrated a significant improvement in relapse-free survival in patients with non-metastatic osteosarcoma, when high dose methotrexate with leucovorin rescue was used in combination with other chemotherapeutic agents following surgical resection of the primary tumor. These studies were not designed to demonstrate the specific contribution of high dose methotrexate/leucovorin rescue therapy to the efficacy of the combination. However, a contribution can be inferred from the reports of objective responses to this therapy in patients with metastatic osteosarcoma, and from reports of extensive tumor necrosis following preoperative administration of this therapy to patients with non-metastatic osteosarcoma.

Pharmacokinetics

Absorption - In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m² or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m² is significantly less, possibly due to a saturation effect.

In leukemic pediatric patients, oral absorption of methotrexate also appears to be dose dependent and has been reported to vary widely (23% to 95%). A twenty-fold difference between highest and lowest peak levels (C_{max}, 0.11 to 2.3 micromolar after a 20 mg/m² dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T_{max}, 0.67 to 4 hrs after a 15 mg/m² dose) and fraction of dose absorbed. The absorption of doses greater than 40 mg/m² has been reported to be significantly less than that of lower doses. Food has been shown to delay absorption and reduce peak concentration. Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes. As in leukemic pediatric patients, a wide interindividual variability in the plasma concentrations of methotrexate has been reported in pediatric patients with JRA. Following oral administration of methotrexate in doses of 6.4 to 11.2 mg/m²/week in pediatric patients with JRA, mean serum concentrations were 0.59 micromolar (range, 0.03 to 1.40) at 1 hour, 0.44 micromolar (range, 0.01 to 1.00) at 2 hours, and 0.29 micromolar (range, 0.08 to 0.58) at 3 hours. In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m²), or for JRA (3.75 to 26.2 mg/m²), the terminal half-life has been reported to range from 0.7 to 5.8 hours or 0.9 to 2.3 hours, respectively.

Distribution - After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40 to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism - After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life - The terminal half-life reported for methotrexate is approximately 3 to 10 hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low-dose antineoplastic therapy (less than 30 mg/m²). For patients receiving high doses of methotrexate, the terminal half-life is 8 to 15 hours.

Excretion - Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80 to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in pediatric patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination. Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustment of leucovorin dosing. Guidelines for monitoring serum methotrexate levels, and for adjustment of leucovorin dosing to reduce the risk of methotrexate toxicity, are provided below in **DOSAGE AND ADMINISTRATION**.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

INDICATIONS AND USAGE

Neoplastic Diseases: Methotrexate is indicated in the treatment of gestational choriocarcinoma, choriodarcinoma destruens and hydatidiform mola.

In acute lymphocytic leukemia, methotrexate is indicated in the prophylaxis of meningeal leukemia and is used in maintenance therapy in combination with other chemotherapeutic agents. Methotrexate is also indicated in the treatment of meningeal leukemia.

Methotrexate is used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides (cutaneous T cell lymphoma), and lung cancer, particularly squamous cell and small cell types. Methotrexate is also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin's lymphoma.

Methotrexate in high dose followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with non-metastatic osteosarcoma who have undergone surgical resection or amputation for the primary tumor.

Psoriasis: Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, *but only when the diagnosis has been established, as by a biopsy and/or after dermatologic consultation*. It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis: Methotrexate is indicated in the management of selected adults with severe, active rheumatoid arthritis (ACR criteria), or children with active polyarticular-course juvenile rheumatoid arthritis, who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose nonsteroidal anti-inflammatory agents (NSAIDs).

Aspirin, NSAIDs, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. (See **PRECAUTIONS, Drug Interactions.**) Steroids may be reduced gradually in patients who respond to methotrexate. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

CONTRAINDICATIONS

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (see **PRECAUTIONS**) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of 3 months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients (see Boxed **WARNINGS**).

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

Patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia, should not receive methotrexate.

Patients with known hypersensitivity to methotrexate should not receive the drug.

WARNINGS

See Boxed WARNINGS.

Methotrexate formulations and diluents containing preservatives must not be used for intrathecal or high dose methotrexate therapy.

PRECAUTIONS

General: Methotrexate has the potential for serious toxicity (see Boxed **WARNINGS**). Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyzer. (See **OVERDOSAGE**.) If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Some of the effects mentioned under **ADVERSE REACTIONS**, such as dizziness and lethgus, may affect the ability to drive or operate machinery.

Information for Patients: Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Prescriptions should not be written or refilled on a PRN basis.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Laboratory Tests: Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During therapy of rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: hematology at least monthly, renal function and liver function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. *During initial or changing doses*, or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation. (See **PRECAUTIONS, Organ System Toxicity**, *Hepatic*.)

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

Drug Interactions: Nonsteroidal anti-inflammatory drugs should not be administered prior to or concomitantly with the high doses of methotrexate, such as used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs or salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

In the treatment of patients with osteosarcoma, caution must be exercised if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g., cisplatin).

Methotrexate increases the plasma levels of mercaptopurine. The combination of methotrexate and mercaptopurine may therefore require dose adjustment.

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad-spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxins (e.g., azathioprine, retinoids, sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased folate/vit B12 absorption and/or additive antifolate effect.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active anti-lymphoma treatment. Benefits should be weighed against the potential risks before using methotrexate alone or in combination with other drugs, especially in pediatric patients or young adults. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy, Teratogenic Effects, Pregnancy Category X: Psoriasis and rheumatoid arthritis: Methotrexate is in Pregnancy Category X (See **CONTRAINDICATIONS**).

Nursing Mothers: See **CONTRAINDICATIONS**.

Pediatric Use: Safety and effectiveness in pediatric patients have been established only in cancer chemotherapy and in polyarticular-course juvenile rheumatoid arthritis.

Published clinical studies evaluating the use of methotrexate in children and adolescents (i.e., patients 2 to 16 years of age) with JRA demonstrated safety comparable to that observed in adults with rheumatoid arthritis. (See **CLINICAL PHARMACOLOGY, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**.)

Methotrexate injectable formulations containing the preservative benzyl alcohol are not recommended for use in neonates. There have been reports of fatal "gasping syndrome" in neonates (children less than one month of age) following the administration of intravenous solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m²). (See **PRECAUTIONS, Organ System Toxicity**, *Neurologic*.)

Geriatric Use: Clinical studies of methotrexate did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic and renal function, decreased folate stores, concomitant disease or other drug therapy (i.e., that interfere with renal function, methotrexate or folate metabolism) in this population (see **PRECAUTIONS, Drug Interactions**). Since decline in renal function may be associated with increases in adverse events and serum creatinine measurements may over estimate renal function in the elderly, more accurate methods (i.e., creatinine clearance) should be considered. Serum methotrexate levels may also be helpful. Elderly patients should be closely monitored for early signs of hepatic, bone marrow and renal toxicity. In chronic use situations, certain toxicities may be reduced by folate supplementation. Post-marketing experience suggests that the occurrence of bone marrow suppression, thrombocytopenia, and pneumonitis may increase with age. See Boxed **WARNINGS** and **ADVERSE REACTIONS**.

Organ System Toxicity: *Gastrointestinal* - If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Hematologic - Methotrexate can suppress hematopoiesis and cause anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment, the drug should be used with caution, if at all. In controlled clinical trials in rheumatoid arthritis (*n*=128), leukopenia (WBC <3000/mm³) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm³) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic - Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes, and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2 to 4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug. mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation are relatively common preitherapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1.5 g) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Liver function tests should be performed at baseline and at 4 to 8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored as per recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb, or IV).

Infection or Immunologic States - Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunizations in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Neurologic - There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had cranispinal irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m²). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation. Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dosage regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, transient blindness, seizures and coma. The exact cause is unknown.

After the intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by paraparesis/paraplegia associated with involvement with one or more spinal nerve roots; chronic leukoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, seizures and coma. This condition can be progressive and even fatal.

Pulmonary - Pulmonary symptoms (especially a dry, nonproductive cough) or a nonspecific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection (including pneumonia) needs to be excluded. This lesion can occur at all dosages.

Renal – Methotrexate may cause renal damage that may lead to acute renal failure. High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin - Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple, low, intermediate or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Other Precautions - Methotrexate should be used with extreme caution in the presence of debility.

Methotrexate exits slowly from third space compartments (e.g., pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

ADVERSE REACTIONS

IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN THE PRECAUTIONS SECTION. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Alimentary System - gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hemorrhagic enteritis, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Blood and Lymphatic System Disorders - suppressed hematopoiesis, anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, eosinophilia, lymphadenopathy and lymphoproliferative disorders (including reversible). Hypogammaglobulinemia has been reported rarely.

Cardiovascular - pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System - headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy.

Hepatobiliary Disorders - hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, hepatic failure, decrease in serum albumin, liver enzyme elevations.

Infection - There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common opportunistic infection. There have also been reports of infections, pneumonia, cytomegalovirus infection, including cytomegaloviral pneumonia, sepsis, fatal sepsis, nocardiosis; histoplasmosis, cryptococcosis, *Herpes zoster*, *H. simplex* hepatitis, and disseminated *H. simplex*.

Musculoskeletal System - stress fracture.

Ophthalmic - conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System – respiratory fibrosis, respiratory failure, alveolitis, interstitial pneumonitis; deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin – erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, skin ulceration, and exfoliative dermatitis.

Urogenital System - severe nephropathy or renal failure, azotemia, cystitis, hematuria, proteinuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal death, fetal defects.

Other rare reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, reversible lymphomas, tumor lysis syndrome, soft tissue necrosis, and osteonecrosis. Anaphylactoid reactions have been reported.

Adverse Reactions in Double-Blind Rheumatoid Arthritis Studies: The approximate incidences of methotrexate-attributed (i.e., placebo rate subtracted) adverse reactions in 12 to 18 week double-blind studies of patients (n=128) with rheumatoid arthritis treated with low-dose oral (7.5 to 15 mg/wk) pulse methotrexate, are listed below. Virtually all of these patients were on concomitant nonsteroidal anti-inflammatory drugs and some were also taking low dosages of corticosteroids. Hepatic histology was not examined in these short-term studies. (See **PRECAUTIONS**.)

Incidence greater than 10%: Elevated liver function tests 15%, nausea/vomiting 10%.

Incidence 3% to 10%: Stomatitis, thrombocytopenia (platelet count less than 100,000/mm^3).

Incidence 1% to 3%: Rash/pruritus/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm^3), pancytopenia, dizziness.

Two other controlled trials of patients (n=880) with Rheumatoid Arthritis on 7.5 mg to 15 mg/wk oral doses showed an incidence of interstitial pneumonitis of 1%. (See **PRECAUTIONS**.)

Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistaxis, fever, infection, sweating, tinnitus, and vaginal discharge.

Adverse Reactions in Psoriasis: There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969, and Nyfors, 1978) describing large series (n=204, 249) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With the exception of alopecia, photosensitivity, and "burning of skin lesions" (each 3 to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies. Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: *Am Acad Dermatol* 35: 835-838, 1996).

Adverse Reactions in JRA Studies: The approximate incidences of adverse reactions reported in pediatric patients with JRA treated with oral, weekly doses of methotrexate (5 to 20 mg/m^2/wk or 0.1 to 0.65 mg/kg/wk) were as follows (virtually all patients were receiving concomitant nonsteroidal anti-inflammatory drugs, and some also were taking low doses of corticosteroids): elevated liver function tests, 14%; gastrointestinal reactions (e.g., nausea, vomiting, diarrhea), 11%; stomatitis, 2%; leukopenia, 2%; headache, 1.2%; alopecia, 0.3%; dizziness, 0.4%; and rash, 0.2%. Although there is experience with dosing up to 30 mg/m^2/wk in JRA, the published data for doses above 20 mg/m^2/wk are too limited to provide reliable estimates of adverse reaction rates.

OVERDOSAGE

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered methotrexate or methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis have been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer (Wall, SM et al: *Am J Kidney Dis* 28(6): 846-854, 1996).

Accidental intrathecal overdosage may require intensive systemic support, high-dose systemic leucovorin, alkaline diuresis and rapid CSF drainage and ventricular/lumbar perfusion.

In postmarketing experience, overdose with methotrexate has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose have also been reported.

Reports of oral overdose often indicate accidental daily administration instead of weekly (single or divided doses). Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacologic doses, particularly hematologic and gastrointestinal reaction. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anemia were also reported.

Symptoms of intrathecal overdose are generally central nervous system (CNS) symptoms, including headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy. In some cases, no symptoms were reported. There have been reports of death following intrathecal overdose. In these cases, cerebellar herniation associated with increased intracranial pressure, and acute toxic encephalopathy have also been reported.

There are published case reports of intravenous and intrathecal carboxypeptidase G2 treatment to reduce clearance of methotrexate in cases of overdose.

DOSAGE AND ADMINISTRATION

Neoplastic Diseases: Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained. Methotrexate sodium (preservative free) injectable products may be given by the intramuscular, intravenous, intra-arterial, or intrathecal route. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Choriocarcinoma and Similar Trophoblastic Diseases - Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a 5-day course. Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24-hour quantitative analysis of urinary chorionic gonadotropin (hCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Choriadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukemia - Acute lymphoblastic leukemia in pediatric patients and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m^2 in combination with 60 mg/m^2 of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m^2. It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should be familiar with the new advances in antileukemic therapy.

Meningeal Leukemia - In the treatment or prophylaxis of meningeal leukemia, methotrexate must be administered intrathecally. Preservative free methotrexate is diluted to a concentration of 1 mg/mL with an appropriate sterile, preservative free medium such as 0.9% Sodium Chloride Injection, USP.

The cerebrospinal fluid volume is dependent on age and not body surface area. The CSF is at 40% of the adult volume at birth and reaches the adult volume in several years.

Intrathecal methotrexate administration at a dose of 12 mg/m^2 (maximum 15 mg) has been reported to result in low CSF methotrexate concentrations and reduced efficacy in pediatric patients and high concentrations and neurotoxicity in adults. The following dosage regimen is based on age instead of body surface area.

Age (years)	Dose (mg)
<1	6
1	8
2	10
3 or older	12

In one study in patients under the age of 40, this dosage regimen appeared to result in more consistent CSF methotrexate concentrations and less neurotoxicity. Another study in pediatric patients with acute lymphocytic leukemia compared the above regimen to a dose of 12 mg/m^2 (maximum 15 mg). A significant reduction in the rate of CNS relapse was observed in the group whose dose was based on age.

Because the CSF volume and turnover may decrease with age, a dose reduction may be indicated in elderly patients.

For the treatment of meningeal leukemia, intrathecal methotrexate may be given at intervals of 2 to 5 days. However, administration at intervals of less than 1 week may result in increased subacute toxicity. Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal. At this point one additional dose is advisable. For prophylaxis against meningeal leukemia, the dosage is the same as for treatment except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical literature.

Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character. Large doses may cause convulsions. Methotrexate given by the intrathecal route appears significantly in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic antileukemic therapy with the drug should be appropriately adjusted, reduced or discontinued. Focal leukemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas - In Burkitt's Tumor, Stages I–II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis Fungoides (cutaneous T cell lymphoma) – Therapy with methotrexate as a single agent appears to produce clinical responses in up to 50% of patients treated. Dosage in early stages is usually 5 to 50 mg once weekly. Dose reduction or cessation is guided by patient response and hematologic monitoring. Methotrexate has also been administered twice weekly in doses ranging from 15 to 37.5 mg in patients who have responded poorly to weekly therapy. Combination chemotherapy regimens that include intravenous methotrexate administered at higher doses with leucovorin rescue have been utilized in advanced stages of the disease.

Osteosarcoma - An effective adjuvant chemotherapy regimen requires the administration of several cytotoxic chemotherapeutic agents. In addition to high-dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin, and the combination of bleomycin, cyclophosphamide and dactinomycin (BCD) in the doses and schedule shown in the table below. The starting dose for high dose methotrexate treatment is 12 grams/m^2. If this dose is not sufficient to produce a peak serum methotrexate concentration of 1,000 micromolar (10-3 mol/L) at the end of the methotrexate infusion, the dose may be escalated to 15 grams/m^2 in subsequent treatments. If the patient is vomiting or is unable to tolerate oral medication, leucovorin is given IV or IM at the same dose and schedule.

Drug*	Dose*	Treatment Week After Surgery
Methotrexate	12 g/m^2 IV as 4 hour infusion (starting dose)	4,5,8,7,11,12,15, 16,29,30,44,45
Leucovorin	15 mg orally every six hours for 10 doses starting at 24 hours after start of methotrexate infusion.	
Doxorubicin† as a single drug	30 mg/m^2/day IV x 3 days	8,17
Doxorubicin† Cisplatin†	50 mg/m^2 IV 100 mg/m^2 IV	22,23,33,36 29,23,33,36
Bleomycin† Cyclophosphamide† Dactinomycin†	15 units/m^2 IV x 2 days 600 mg/m^2 IV x 2 days 0.6 mg/m^2 IV x 2 days	2,13,26,39,42 2,13,26,39,42 2,13,26,39,42

*Link MP, Goorin AM, Miser AW, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J of Med* 1986; 314(No.25): 1600-1606.

†See each respective package insert for full prescribing information. Dosage modifications may be necessary because of drug-induced toxicity.

When these higher doses of methotrexate are to be administered, the following safety guidelines should be closely observed.

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

1. Administration of methotrexate should be delayed until recovery if:
   - the WBC count is less than 1500/microliter
   - the neutrophil count is less than 200/microliter
   - the platelet count is less than 75,000/microliter
   - the serum bilirubin level is greater than 1.2 mg/dL
   - the SGPT level is greater than 450 U
   - mucositis is present, until there is evidence of healing
   - persistent pleural effusion is present; this should be drained dry prior to infusion.
2. Adequate renal function must be documented.
   a. Serum creatinine must be normal, and creatinine clearance must be greater than 60 mL/min, before initiation of therapy.
   b. Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50% or more compared to a prior value, the creatinine clearance must be measured and documented to be greater than 60 mL/min (even if the serum creatinine is still within the normal range).
3. Patients must be well hydrated, and must be treated with sodium bicarbonate for urinary alkalinization.
   a. Administer 1,000 mL/m^2 of intravenous fluid over 6 hours prior to initiation of the methotrexate infusion. Continue hydration at 125 mL/m^2/hr (3 liters/m^2/day) during the methotrexate infusion, and for 2 days after the infusion has been completed.
   b. Alkalinize urine to maintain pH above 7.0 during methotrexate infusion and leucovorin calcium therapy. This can be accomplished by the administration of sodium bicarbonate orally or by incorporation into a separate intravenous solution.
4. Repeat serum creatinine and serum methotrexate 24 hours after starting methotrexate and at least once daily until the methotrexate level is below 5x10-8 mol/L (0.05 micromolar).
5. The table below provides guidelines for leucovorin calcium dosage based upon serum methotrexate levels. (See table below.‡)

Patients who experience delayed early methotrexate elimination are likely to develop nonreversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved. If necessary, acute, intermittent hemodialysis with a high-flux dialyzer may also be beneficial in these patients.

6. Some patients will have abnormalities in methotrexate elimination, or abnormalities in renal function following methotrexate administration, which are significant but less severe than the abnormalities described in the table below. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g., medications which may interfere with methotrexate binding to serum albumin, or elimination) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

Psoriasis, Rheumatoid Arthritis, and Juvenile Rheumatoid Arthritis

Adult Rheumatoid Arthritis: Recommended Starting Dosage Schedules

1. Single oral doses of 7.5 mg once weekly.†
2. Divided oral dosages of 2.5 mg at 12 hour intervals for 3 doses given as a course once weekly.†

†Methotrexate Sodium Tablets for oral administration are available.

Polyarticular-Course Juvenile Rheumatoid Arthritis: The recommended starting dose is 10 mg/m^2 given once weekly.

For either adult RA or polyarticular-course JRA dosages may be adjusted gradually to achieve an optimal response. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk in adults. Although there is experience with doses up to 30 mg/m^2/wk in children, there are too few published data to assess how doses over 20 mg/m^2/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m^2/wk (0.65 to 1 mg/kg/wk) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

The optimal duration of therapy is unknown. Limited data available from long-term studies in adults indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

The patient should be fully informed of the risks involved and should be under constant supervision of the physician. (See **Information for Patients** under **PRECAUTIONS**.) Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy (see **PRECAUTIONS**). Appropriate steps should be taken to avoid conception during methotrexate therapy (see **PRECAUTIONS** and **CONTRAINDICATIONS**).

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to this regular dosing schedule to detect any extreme sensitivity to adverse effects (see **ADVERSE REACTIONS**). Maximal myelosuppression usually occurs in 7 to 10 days.

Psoriasis: Recommended Starting Dose Schedules

1. Weekly single oral, IM or IV dosage schedule: 10 to 25 mg per week until adequate response is achieved.†
2. Divided oral dosage schedule: 2.5 mg at 12 hour intervals for three doses.†

†Methotrexate Sodium Tablets for oral administration are available.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Reconstitution of Lyophilized Powders: Reconstitute immediately prior to use.

Methotrexate for injection should be reconstituted with an appropriate sterile, preservative free medium such as 5% dextrose solution, USP or sodium chloride injection, USP. **The 1 gram vial should be reconstituted with 15.4 mL to a concentration of 50 mg/mL.** When high doses of methotrexate are administered by IV infusion, the total dose is diluted in 5% dextrose solution, USP.

For intrathecal injection, reconstitute to a concentration of 1 mg/mL with an appropriate sterile, preservative free medium such as sodium chloride injection, USP.

Dilution Instructions for Liquid Methotrexate Injection: Isotonic liquid, preservative free, for single use only.

If desired, the solution may be further diluted immediately prior to use with an appropriate sterile, preservative free medium such as 5% dextrose solution, USP or sodium chloride injection, USP.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Methotrexate Injection, USP (preservative free) is supplied in a single-dose vial containing 25 mg/mL of methotrexate as the base in the following package strengths:

NDC 55390-031-10	50 mg in 2 mL (10 vials to a carton)
NDC 55390-032-10	100 mg in 4 mL (10 vials to a carton)
NDC 55390-033-10	200 mg in 8 mL (10 vials to a carton)
NDC 55390-034-10	250 mg in 10 mL (10 vials to a carton)

Methotrexate for Injection, USP (preservative free) is supplied in a 1 gram, single-dose vial of lyophilized powder containing 1 gram methotrexate as the base in the following package strength:

NDC 55390-143-01	1 gram Vial (individually boxed)

Store at room temperature 20° to 25°C (68° to 77°F). See USP controlled room temperature. **Protect from light**.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*, March 15, 1985.

3. National Study Commission on Cytotoxic Exposure–Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc. D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Ave., Boston, Massachusetts 02115.

4. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia* 1: 426-428, 1983.

5. Jones RB et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. *CA-A Cancer Journal for Clinicians*: Sept/Oct, 258-263, 1983.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 47:1033-1049, 1990.

7. Controlling occupational exposure to hazardous drugs (OSHA Work-Practice Guidelines). *AM J Health Syst Pharm* 1996; 53: 1669-1685.

Manufactured by
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Bedford, OH 44146

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Bedford Laboratories™
Bedford, OH 44146

Dis-MTX-P07

LEUCOVORIN RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF METHOTREXATE

Clinical Situation	Laboratory Findings	Leucovorin Dosage and Duration
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours.	15 mg PO, IM or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.	Continue 15 mg PO, IM or IV q 6 hours, until methotrexate level is less than 0.05 micromolar.
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury	Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration; OR, a 100% or greater increase in serum creatinine level at 24 hours following methotrexate administration (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL or more).	150 mg IV q 3 hours, until methotrexate level is less than 1 micromolar; then 15 mg IV q 3 hours, until methotrexate level is less than 0.05 micromolar.

14.4 Intravenous Immunoglobulin United States Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMUNEX®, Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified, safely and effectively. See full prescribing information for GAMUNEX.

GAMUNEX (Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography Purified) 10% Liquid Preparation

Initial U.S. Approval: 2003

WARNING: ACUTE RENAL DYSFUNCTION and FAILURE

See full prescribing information for complete boxed warning.

- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMUNEX does not contain sucrose.**
- **Administer IGIV products at the minimum concentration available and the minimum infusion rate practicable.**

----------RECENT MAJOR CHANGES----------

- Indications and Usage, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (1.3) 09/2008
- Dosage and Administration, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (2.4) 09/2008
- Dosage and Administration, Primary Humoral Immunodeficiency (2.2) 10/2008

----------INDICATIONS AND USAGE----------

GAMUNEX is an immune globulin intravenous (human), 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI) (1.1)
- Idiopathic Thrombocytopenic Purpura (ITP) (1.2)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (1.3)

----------DOSAGE AND ADMINISTRATION----------

- **Intravenous Use Only**

Indication	Dose	Initial Infusion rate	Maintenance infusion rate (if tolerated)
PI (2.2)	300-600 mg/kg	1 mg/kg/min	8 mg/kg/min Every 3-4 weeks
ITP (2.3)	2 g/kg	1 mg/kg/min	8 mg/kg/min
CIDP (2.4)	loading dose: 2 g/kg maintenance dose: 1 g/kg	2 mg/kg/min	8 mg/kg/min Every 3 weeks

- Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue GAMUNEX if renal function deteriorates. (5.2)
- For patients at risk of renal dysfunction or thrombotic events, administer GAMUNEX at the minimum infusion rate practicable. (5.2)

----------DOSAGE FORMS AND STRENGTHS----------

GAMUNEX is supplied in 1 g, 2.5 g, 5 g, 10 g, or 20 g single use bottles. (3)

1 g	10 mL
2.5 g	25 mL
5 g	50 mL
10 g	100 mL
20 g	200 mL

----------CONTRAINDICATIONS----------

- Anaphylactic or severe systemic reactions to human immunoglobulin (4)
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity (4)

----------WARNINGS AND PRECAUTIONS----------

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Epinephrine should be available immediately to treat any acute severe hypersensitivity reactions. (5.1)
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of developing acute renal failure. (5.2)
- Hyperproteinemia, increased serum viscosity and hyponatremia occur in patients receiving IGIV therapy. (5.3)
- Thrombotic events have occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity. (5.4)
- Aseptic Meningitis Syndrome has been reported with GAMUNEX and other IGIV treatments, especially with high doses or rapid infusion. (5.5)
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration. (5.6)
- IGIV recipients should be monitored for pulmonary adverse reactions (TRALI). (5.7)
- The product is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent. (5.9)

----------ADVERSE REACTIONS----------

- **PI** – Most common drug related adverse reactions during clinical trials were headache and cough. (6.1)
- **ITP** – Most common drug related adverse reactions during clinical trials were headache, vomiting, fever, and nausea. (6.1)
- **CIDP** – Most common drug related adverse reactions during clinical trials were headache and fever. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Talecris Biotherapeutics, Inc. at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- The passive transfer of antibodies may interfere with the response to live viral vaccines. (7)
- The passive transfer of antibodies may confound the results of serological testing. (7)

----------USE IN SPECIFIC POPULATIONS----------

- In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse GAMUNEX at the minimum infusion rate practicable. (8.5)
- Pregnancy: no human or animal data. Use only if clearly needed. (8.1)

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See Section 17 for PATIENT COUNSELING INFORMATION. **Revised: October 2008**

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

Talecris Biotherapeutics, Inc.
FULL PRESCRIBING INFORMATION

Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified

GAMUNEX®

10% Liquid Preparation

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis and death.[1] Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. GAMUNEX does not contain sucrose. Glycine, a natural amino acid, is used as a stabilizer. ***(See Dosage and Administration [2.5] and Warnings and Precautions [5.2] for important information intended to reduce the risk of acute renal failure.)***

1 INDICATIONS AND USAGE

Gamunex is an immune globulin intravenous (human) 10% liquid indicated for the treatment of:

1.1 Primary Humoral Immunodeficiency (PI)

GAMUNEX is indicated as replacement therapy of primary humoral immunodeficiency. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.[2–9]

1.2 Idiopathic Thrombocytopenic Purpura (ITP)

GAMUNEX is indicated in Idiopathic Thrombocytopenic Purpura to rapidly raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery.[10–15]

1.3 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

GAMUNEX is indicated for the treatment of CIDP to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

GAMUNEX consists of 9%–11% protein in 0.16–0.24 M glycine. The buffering capacity of GAMUNEX is 35.0 mEq/L (0.35 mEq/g protein). A dose of 1 g/kg body weight therefore represents an acid load of 0.35 mEq/kg body weight. The total buffering capacity of whole blood in a normal individual is 45–50 mEq/L of blood, or 3.6 mEq/kg body weight.[16] Thus, the acid load delivered with a dose of 1 g/kg of GAMUNEX would be neutralized by the buffering capacity of whole blood alone, even if the dose was infused instantaneously.

2.1 Preparation and Handling

- GAMUNEX should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if turbid.
- Do not freeze. Solutions that have been frozen should not be used.
- The GAMUNEX vial is for single use only. GAMUNEX contains no preservative. Any vial that has been entered should be used promptly. Partially used vials should be discarded.
- GAMUNEX should be infused using a separate line by itself, without mixing with other intravenous fluids or medications the subject might be receiving.
- GAMUNEX is not compatible with saline. If dilution is required, GAMUNEX may be diluted with 5% dextrose in water (D5/W). No other drug interactions or compatibilities have been evaluated.
- Content of vials may be pooled under aseptic conditions into sterile infusion bags and infused within 8 hours after pooling.
- Do not mix with immune globulin intravenous (IGIV) products from other manufacturers.
- Do not use after expiration date.

2.2 Treatment of Primary Humoral Immunodeficiency

As there are significant differences in the half-life of IgG among patients with primary immunodeficiencies, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response.

The dose of GAMUNEX for replacement therapy in primary immune deficiency diseases is 300 to 600 mg/kg body weight (3-6 mL/kg) administered every 3 to 4 weeks. The dosage may be adjusted over time to achieve the desired trough levels and clinical responses.

If a patient routinely receives a dose of less than 400 mg/kg of GAMUNEX every 3 to 4 weeks (less than 4 mL/kg), and is at risk of measles exposure (i.e., traveling to a measles endemic area), administer a dose of at least 400 mg/kg (4 mL/kg) just prior to the expected measles exposure. If a patient has been exposed to measles, a dose of 400 mg/kg (4 mL/kg) should be administered as soon as possible after exposure.

2.3 Treatment of Idiopathic Thrombocytopenic Purpura

GAMUNEX may be administered at a total dose of 2 g/kg, divided in two doses of 1 g/kg (10 mL/kg) given on two consecutive days or into five doses of 0.4 g/kg (4 mL/kg) given on five consecutive days. If after administration of the first of two daily 1 g/kg (10 mL/kg) doses, an adequate increase in the platelet count is observed at 24 hours, the second dose of 1g/kg body weight may be withheld.

Forty-eight ITP subjects were treated with 2 g/kg GAMUNEX, divided in two 1 g/kg doses (10 mL/kg) given on two successive days. With this dose regimen 35/39 subjects (90%) responded with a platelet count from less than or equal to 20 $x10^9$/L to more than or equal to 50 $x10^9$/L within 7 days after treatment.[17]

The high dose regimen (1 g/kg $\times$ 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

2.4 Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

GAMUNEX may be initially administered as a total loading dose of 2 g/kg (20 mL/kg) given in divided doses over two to four consecutive days. GAMUNEX may be administered as a maintenance infusion of 1 g/kg (10 mL/kg) administered over 1 day or divided into two doses of 0.5 g/kg (5 mL/kg) given on two consecutive days, every 3 weeks.

2.5 Administration

GAMUNEX should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if turbid and/or if discoloration is observed.

Only administer intravenously. GAMUNEX should be at room temperature during administration.

Only 18 gauge needles should be used to penetrate the stopper for dispensing product from the 10 mL vial; 16 gauge needles or dispensing pins should only be used with 25 mL vial sizes and larger. Needles or dispensing pins should only be inserted once and be within the stopper area delineated by the raised ring. The stopper should be penetrated perpendicular to the plane of the stopper within the ring.

GAMUNEX® vial size	Gauge of needle to penetrate stopper
10 mL	18 gauge
25, 50, 100, 200 mL	16 gauge

Any vial that has been opened should be used promptly. Partially used vials should be discarded.

If dilution is required, GAMUNEX may be diluted with 5% dextrose in water (D5/W).

Rate of Administration

It is recommended that GAMUNEX should initially be infused at a rate of 0.01 mL/kg per minute (1 mg/kg per minute) for the first 30 minutes. If well-tolerated, the rate may be gradually increased to a maximum of 0.08 mL/kg per minute (8 mg/kg per minute).

Indication	Initial infusion rate (first 30 minutes)	Maximum infusion rate (if tolerated)
PI	1 mg/kg/min	8 mg/kg/min
ITP	1 mg/kg/min	8 mg/kg/min
CIDP	2 mg/kg/min	8 mg/kg/min

Certain severe adverse drug reactions may be related to the rate of infusion. Slowing or stopping the infusion usually allows the symptoms to disappear promptly.

Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue GAMUNEX if renal function deteriorates.

For patients at risk of renal dysfunction or thromboembolic events, administer GAMUNEX at the minimum infusion rate practicable.

Incompatibilities

GAMUNEX is not compatible with saline. If dilution is required, GAMUNEX may be diluted with 5% dextrose in water (D5/W). No other drug interactions or compatibilities have been evaluated.

Shelf Life

GAMUNEX may be stored for 36 months at 2-8°C (36-46°F) from the date of manufacture AND product may be stored at temperatures not to exceed 25°C (77°F) for up to 6 months any time during the 36 month shelf life, after which the product must be immediately discarded.

Special Precautions for Storage

Do not freeze. Frozen product should not be used.

Do not use after expiration date.

3 DOSAGE FORMS AND STRENGTH

GAMUNEX is supplied in 1 g, 2.5 g, 5 g, 10 g, or 20 g single use bottles.

- 1 g in 10 mL solution
- 2.5 g in 25 mL solution
- 5 g in 50 mL solution
- 10 g in 100 mL solution
- 20 g in 200 mL solution

4 CONTRAINDICATIONS

- GAMUNEX is contraindicated in individuals with acute severe hypersensitivity reactions to Immune Globulin (Human).
- GAMUNEX contains trace amounts of IgA. It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity. *(See Description [11])*

5 WARNINGS AND PRECAUTIONS

5.1 Sensitivity

Severe hypersensitivity reactions may occur. In case of hypersensitivity, IGIV infusion should be immediately discontinued and appropriate treatment instituted. Epinephrine should be immediately available for treatment of acute severe hypersensitivity reaction. *(See Patient Counseling Information [17])*

GAMUNEX contains trace amounts of IgA (average 46 micrograms/mL). It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity. *(See Patient Counseling Information [17])*

5.2 Renal Failure

Assure that patients are not volume depleted prior to the initiation of the infusion of IGIV. Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to the initial infusion of GAMUNEX and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered. *(See Patient Counseling Information [17])* For patients judged to be at risk for developing renal dysfunction and/or at risk of developing thrombotic events, it may be prudent to reduce the amount of product infused per unit time by infusing GAMUNEX at a rate less than 8 mg IG/kg/min (0.08 mL/kg/min). *(See Boxed Warning) (See Dosage and Administration [2.5])*

5.3 Hyperproteinemia

Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving IGIV therapy. The hyponatremia is likely to be a pseudohyponatremia as demonstrated by a decreased calculated serum osmolality or elevated osmolar gap. Distinguishing true hyponatremia from pseudohyponatremia is clinically critical, as treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity and a disposition to thromboembolic events.[18]

5.4 Thrombotic Events

Thrombotic events have been reported in association with IGIV.[19–21] Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization and/or known or suspected hyperviscosity. The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

5.5 Aseptic Meningitis Syndrome (AMS)

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with Immune Globulin Intravenous (Human) treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.[22–24] The syndrome usually begins within several hours to two days following IGIV treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cu mm, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. It appears that patients with a history of migraine may be more susceptible. *(See Patient Counseling Information [17])*

5.6 Hemolysis

Immune Globulin Intravenous (Human) (IGIV) products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.[25–27] Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration. IGIV recipients should be monitored for clinical signs and symptoms of hemolysis.[28] If signs and/or symptoms of hemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be done. *(See Patient Counseling Information [17])*

5.7 Transfusion-related Acute Lung Injury (TRALI)

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] in patients administered IGIV.[29] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1-6 hrs after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

IGIV recipients should be monitored for pulmonary adverse reactions. *(See Patient Counseling Information [17])* If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum.

5.8 Volume Overload

The high dose regimen (1 g/kg $\times$ 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

5.9 General

Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Talecris Biotherapeutics, Inc. [1-800-520-2807]. The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient. *(See Patient Counseling Information [17])*

5.10 Laboratory Tests

If signs and/or symptoms of hemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be done.

If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum.

Because of the potentially increased risk of thrombosis, baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

6 ADVERSE REACTIONS

6.1 Adverse Drug Reaction Overview

The most serious adverse reaction observed in clinical study subjects receiving GAMUNEX for PI was an exacerbation of autoimmune pure red cell aplasia in one subject.

The most serious adverse reaction observed in clinical study subjects receiving GAMUNEX for ITP was myocarditis in one subject that occurred 50 days post study drug infusion and was not considered drug related.

The most serious adverse reaction observed in clinical study subjects receiving GAMUNEX for CIDP was pulmonary embolism (PE) in one subject with a history of PE.

The most common drug related adverse reactions observed at a rate $\geq$5% in subjects with PI were headache, cough, injection site reaction, nausea, pharyngitis and urticaria.

The most common drug related adverse reactions observed at a rate $\geq$5% in subjects with ITP were headache, vomiting, fever, nausea, back pain and rash.

The most common drug related adverse reactions observed at a rate $\geq$5% in subjects with CIDP were headache, fever, chills, hypertension, rash, nausea and asthenia.

6.2 Clinical Trials Adverse Drug Reactions

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

Adverse events similar to those previously reported with the administration of intravenous and intramuscular immunoglobulin products may occur. Cases of reversible aseptic meningitis, migraine, isolated cases of reversible hemolytic anemia and reversible increases in liver function tests have been observed with GAMUNEX. Immediate anaphylactic reactions can possibly occur (<0.01%). Epinephrine should be available for treatment of any acute anaphylactoid reaction. *(see Warnings and Precautions [5.1])*

Treatment of Primary Humoral Immunodeficiency

The following table shows the number of subjects treated with GAMUNEX in clinical trials to study PI, and the reason for discontinuation due to adverse events:

Table 1: Reasons for Discontinuation Due to Adverse Events: All PI Studies

Study Number	Number of Subjects Treated with GAMUNEX®	Number of Subjects Discontinued Due to Adverse Events	Adverse Event
100152	18	0	-----
100174	20	1	Coombs negative hypochromic anemia*
100175	87	1	Autoimmune pure red cell aplasia*

* Both events were considered unrelated to study drug as per the investigator.

In study 100175, 9 subjects in each treatment group were pretreated with non-steroidal medication prior to infusion. Generally, diphenhydramine and acetaminophen were used.

Any adverse events in trial 100175, irrespective of the causality assessment, are given in the following table.

Table 2: Subjects with At Least One Adverse Event *Irrespective of Causality* (Study 100175)

Adverse Event	GAMUNEX® No. of subjects: 87 No. of subjects with AE (percentage of all subjects)	GAMIMUNE® N, 10% No. of subjects: 85 No. of subjects with AE (percentage of all subjects)
Cough increased	47 (54%)	46 (54%)
Rhinitis	44 (51%)	45 (53%)
Pharyngitis	36 (41%)	39 (46%)
Headache	22 (25%)	28 (33%)
Fever	24 (28%)	27 (32%)
Diarrhea	24 (28%)	27 (32%)
Asthma	25 (29%)	17 (20%)
Nausea	17 (20%)	22 (26%)
Ear Pain	16 (18%)	12 (14%)
Asthenia	9 (10%)	13 (15%)

The subset of drug related adverse events in trial 100175 reported by at least 5% of subjects during the 9-month treatment are given in the following table.

Table 3: Subjects with At Least One *Drug Related* Adverse Event (Study 100175)

Drug Related Adverse Event	GAMUNEX® No. of subjects: 87 No. of subjects with drug related AE (percentage of all subjects)	GAMIMUNE® N, 10% No. of subjects: 85 No. of subjects with drug related AE (percentage of all subjects)
Headache	7 (8%)	8 (9%)
Cough increased	6 (7%)	4 (5%)
Injection site reaction	4 (5%)	7 (8%)
Nausea	4 (5%)	4 (5%)
Pharyngitis	4 (5%)	3 (4%)
Urticaria	4 (5%)	1 (1%)

Adverse events, which were reported by at least 5% of subjects, were also analyzed by frequency and in relation to infusions administered. The analysis is displayed in the following table.

Table 4: Adverse Event Frequency (Study 100175)

Adverse Event		GAMUNEX® No. of infusions: 825 No. of AE (percentage of all infusions)	GAMIMUNE® N, 10% No. of infusions: 865 No. of AE (percentage of all infusions)
Cough increased	All	154 (18.7%)	148 (17.1%)
	Drug related	*14 (1.7%)*	*11 (1.3%)*
Pharyngitis	All	96 (11.6%)	99 (11.4%)
	Drug related	*7 (0.8%)*	*9 (1.0%)*
Headache	All	57 (6.9%)	69 (8.0%)
	Drug related	*7 (0.8%)*	*11 (1.3%)*
Fever	All	41 (5.0%)	65 (7.5%)
	Drug related	*1 (0.1%)*	*9 (1.0%)*
Nausea	All	31 (3.8%)	43 (5.0%)
	Drug related	*4 (0.5%)*	*4 (0.5%)*
Urticaria	All	5 (0.6%)	8 (0.9%)
	Drug related	*4 (0.5%)*	*5 (0.6%)*

The mean number of adverse events per infusion that occurred during or on the same day as an infusion was 0.21 in both the GAMUNEX and GAMIMUNE® N, Immune Globulin Intravenous (Human), 10%, treatment groups.

In all three trials in primary humoral immundeficiencies, the maximum infusion rate was 0.08 mL/kg/min (8 mg/kg/min). The infusion rate was reduced for 11 of 222 exposed subjects (7 GAMUNEX, 4 GAMIMUNE N, 10%) at 17 occasions. In most instances, mild to moderate hives/urticaria, itching, pain or reaction at infusion site, anxiety or headache was the main reason. There was one case of severe chills. There were no anaphylactic or anaphylactoid reactions to GAMUNEX or GAMIMUNE N, 10%.

In trial 100175, serum samples were drawn to monitor the viral safety at baseline and one week after the first infusion (for parvovirus B19), eight weeks after first and fifth infusion, and 16 weeks after the first and fifth infusion of IGIV (for hepatitis C) and at any time of premature discontinuation of the study. Viral markers of hepatitis C, hepatitis B, HIV-1, and parvovirus B19 were monitored by nucleic acid testing (NAT, Polymerase Chain Reaction (PCR)), and serological testing. There were no treatment emergent findings of viral transmission for either GAMUNEX or GAMIMUNE N, 10%.[30-32]

Treatment of Idiopathic Thrombocytopenic Purpura

The following table shows the number of subjects treated with GAMUNEX in clinical trials to study ITP, and the reason for discontinuation due to adverse events:

Table 5: Reasons for Discontinuation Due to Adverse Events: All ITP Studies

Study Number	Number of Subjects Treated with GAMUNEX®	Number of Subjects Discontinued Due to Adverse Events	Adverse Event
100213	28	1	Hives
100176	48	1	Headache, Fever, Vomiting

One subject, a 10-year-old boy, died suddenly from myocarditis 50 days after his second infusion of GAMUNEX. The death was judged to be unrelated to GAMUNEX.

No pre-medication with corticosteroids was permitted by the protocol. Twelve (12) ITP subjects treated in each treatment group were pretreated with medication prior to infusion. Generally, diphenhydramine and/or acetaminophen were used. More than 90% of the observed drug related adverse events were of mild to moderate severity and of transient nature.

The infusion rate was reduced for 4 of the 97 exposed subjects (1 GAMUNEX, 3 GAMIMUNE N, 10%) on 4 occasions. Mild to moderate headache, nausea, and fever were the reported reasons. There were no anaphylactic or anaphylactoid reactions to GAMUNEX or GAMIMUNE N, 10%.

Any adverse events in trial 100176, irrespective of the causality assessment, reported by at least 5% of subjects during the 3-month trial are given in the following table.

Table 6: Subjects with At Least One Adverse Event *Irrespective of Causality* (Study 100176)

Adverse Event	GAMUNEX® No. of subjects: 48 No. of subjects with AE (percentage of all subjects)	GAMIMUNE® N, 10% No. of subjects: 49 No. of subjects with AE (percentage of all subjects)
Headache	28 (58%)	30 (61%)
Ecchymosis, Purpura	19 (40%)	25 (51%)
Hemorrhage (All systems)	14 (29%)	16 (33%)
Epistaxis	11 (23%)	12 (24%)
Petechiae	10 (21%)	15 (31%)
Fever	10 (21%)	7 (14%)
Vomiting	10 (21%)	10 (20%)
Nausea	10 (21%)	7 (14%)
Thrombocytopenia	7 (15%)	8 (16%)
Accidental injury	6 (13%)	8 (16%)
Rhinitis	6 (13%)	6 (12%)
Pharyngitis	5 (10%)	5 (10%)
Rash	5 (10%)	6 (12%)
Pruritis	4 (8%)	1 (2%)
Asthenia	3 (6%)	5 (10%)
Abdominal Pain	3 (6%)	4 (8%)
Arthralgia	3 (6%)	6 (12%)
Back Pain	3 (6%)	3 (6%)
Dizziness	3 (6%)	3 (6%)
Flu Syndrome	3 (6%)	3 (6%)
Neck Pain	3 (6%)	1 (2%)
Anemia	3 (6%)	0 (0%)
Dyspepsia	3 (6%)	0 (0%)

The subset of drug related adverse events in trial 100176 reported by at least 5% of subjects during the 3-month trial are given in the following table.

Table 7: Subjects with At Least One *Drug Related* Adverse Event (Study 100176)

Drug Related Adverse Event	GAMUNEX® No. of subjects: 48 No. of subjects with drug related AE (percentage of all subjects)	GAMIMUNE® N, 10% No. of subjects: 49 No. of subjects with drug related AE (percentage of all subjects)
Headache	24 (50%)	24 (49%)
Vomiting	6 (13%)	8 (16%)
Fever	5 (10%)	5 (10%)
Nausea	5 (10%)	4 (8%)
Back Pain	3 (6%)	2 (4%)
Rash	3 (6%)	0 (0%)

Serum samples were drawn to monitor the viral safety of the ITP subjects at baseline, nine days after the first infusion (for parvovirus B19), and 3 months after the first infusion of IGIV and at any time of premature discontinuation of the study. Viral markers of hepatitis C, hepatitis B, HIV-1, and parvovirus B19 were monitored by nucleic acid testing (NAT, PCR), and serological testing. There were no treatment related emergent findings of viral transmission for either GAMUNEX®, Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified, or GAMIMUNE® N, Immune Globulin Intravenous (Human), 10%.[17]

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

In study 100538, 113 subjects were exposed to GAMUNEX and 95 were exposed to Placebo. *(See Clinical Studies [14.3])* As a result of the study design, the drug exposure with GAMUNEX was almost twice that of Placebo, with 1096 GAMUNEX infusions versus 575 Placebo infusions. Therefore, adverse reactions are reported per infusion (represented as frequency) to correct for differences in drug exposure between the 2 groups. The majority of loading-doses were administered over 2 days. The majority of maintenance-doses were administered over 1 day. Infusions were administered in the mean over 2.7 hours.

The following table shows the numbers of subjects per treatment group in the CIDP clinical trial, and the reason for discontinuation due to adverse events:

Table 8: Reasons for Discontinuation Due to Adverse Events: CIDP

Number of Subjects		Number of Subjects Discontinued due to Adverse Events	Adverse Event
GAMUNEX®	113	3 (2.7%)	Urticaria, Dyspnea, Bronchopneumonia
Placebo	95	2 (2.1%)	Cerebrovascular Accident, Deep Vein Thrombosis

Adverse events reported by at least 5% of subjects in any treatment group irrespective of causality are shown in the following table.

Table 9: Subjects with At Least One Adverse Event *Irrespective of Causality* (Study 100538)

MedDRA Preferred Term [a]	GAMUNEX® No. of subjects: 113			Placebo No. of subjects: 95		
	No. of Subjects (%)	No. of Adverse Events	Incidence density [b]	No. of Subjects (%)	No. of Adverse Events	Incidence density [b]
Any Adverse Event	85 (75)	377	0.344	45 (47)	120	0.209
Headache	36 (32)	57	0.052	8 (8)	15	0.026
Pyrexia (fever)	15 (13)	27	0.025	0	0	0
Hypertension	10 (9)	20	0.018	4 (4)	6	0.010
Rash	8 (7)	13	0.012	1 (1)	1	0.002
Arthralgia	8 (7)	11	0.010	1 (1)	1	0.002
Asthenia	9 (8)	10	0.009	3 (3)	4	0.007
Chills	9 (8)	10	0.009	0	0	0
Back pain	9 (8)	10	0.009	3 (3)	3	0.005
Nausea	7 (6)	9	0.008	3 (3)	3	0.005
Dizziness	7 (6)	3	0.006	1 (1)	1	0.002
Influenza	6 (5)	6	0.005	2 (2)	2	0.003

a Reported in $\geq$5% of subjects in any treatment group irrespective of causality.

b Calculated by the total number of adverse events divided by the number of infusions received (1096 for GAMUNEX and 575 for Placebo)

Drug-related adverse events reported by at least 5% of subjects in any treatment group are reported in the table below. The most common drug-related events with GAMUNEX were headache and pyrexia:

Table 10: Subjects with At Least One Drug Related Adverse Event (Study 100538)

MedDRA Preferred Term [a]	GAMUNEX® No. of subjects: 113			Placebo No. of subjects: 95		
	No. of Subjects (%)	No. of Adverse Events	Incidence density [b]	No. of Subjects (%)	No. of Adverse Events	Incidence density [b]
Any drug-related adverse event	62 (55)	194	0.177	16 (17)	25	0.043
Headache	31 (27)	44	0.040	6 (6)	7	0.012
Pyrexia (fever)	15 (13)	26	0.024	0	0	0
Chills	8 (7)	9	0.008	0	0	0
Hypertension	7 (6)	16	0.015	3 (3)	3	0.005
Rash	6 (5)	8	0.007	1 (1)	1	0.002
Nausea	6 (5)	7	0.006	3 (3)	3	0.005
Asthenia	6 (5)	6	0.005	0	0	0

a Reported in $\geq$5% of subjects in any treatment group.

b Calculated by the total number of adverse events divided by the number of infusions received (1096 for GAMUNEX and 575 for Placebo)

Laboratory Abnormalities

During the course of the clinical program, ALT and AST elevations were identified in some subjects.

- For ALT, in the primary humoral immunodeficiency (PI) study (100175) treatment emergent elevations above the upper limit of normal were transient and observed among 14/80 (18%) of subjects in the GAMUNEX group versus 5/88 (6%) of subjects in the GAMIMUNE N, 10% group ($p = 0.026$).
- In the ITP study which employed a higher dose per infusion, but a maximum of only two infusions, the reverse finding was observed among 3/44 (7%) of subjects in the GAMUNEX group versus 8/43 (19%) of subjects in the GAMIMUNE N, 10% group ($p = 0.118$).
- In the CIDP study (100538), 15/113 (13%) of subjects in the GAMUNEX group and 7/95 (7%) in the Placebo group ($p=0.168$) had a treatment emergent transient elevation of ALT.

Elevations of ALT and AST were generally mild (<3 times upper limit of normal), transient, and were not associated with obvious symptoms of liver dysfunction.

GAMUNEX may contain low levels of anti-Blood Group A and B antibodies primarily of the IgG_4 class. Direct antiglobulin tests (DAT or direct Coombs tests), which are carried out in some centers as a safety check prior to red blood cell transfusions, may become positive temporarily. Hemolytic events not associated with positive DAT findings were observed in clinical trials.[17, 30–33]

6.3 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

GAMUNEX Postmarketing Experience

The following adverse reactions have been identified and reported during the post marketing use of GAMUNEX:

- *Hematologic*: Hemolytic anemia
- *Infections and Infestations*: Aseptic meningitis

General

The following adverse reactions have been identified and reported during the post marketing use of IGIV products[34]:

- *Respiratory*: Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- *Cardiovascular*: Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological*: Coma, loss of consciousness, seizures/convulsions, tremor
- *Integumentary*: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- *Hematologic*: Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs test)
- *General/Body as a Whole*: Pyrexia, rigors
- *Musculoskeletal*: Back pain
- *Gastrointestinal*: Hepatic dysfunction, abdominal pain

7 DRUG INTERACTIONS

GAMUNEX may be diluted with 5% dextrose in water (D5/W). Admixtures of GAMUNEX with other drugs and intravenous solutions have not been evaluated. It is recommended that GAMUNEX be administered separately from other drugs or medications which the patient may be receiving. The product should not be mixed with IGIVs from other manufacturers.

The infusion line may be flushed before and after administration of GAMUNEX with 5% dextrose in water.

Various passively transferred antibodies in immunoglobulin preparations can confound the results of serological testing.

Antibodies in GAMUNEX may interfere with the response to live viral vaccines such as measles, mumps and rubella. Physicians should be informed of recent therapy with IGIVs, so that administration of live viral vaccines, if indicated, can be appropriately delayed 3 or more months from the time of IGIV administration. *(See Patient Counseling Information [17])*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with GAMUNEX. It is not known whether GAMUNEX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. GAMUNEX should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

GAMUNEX has not been evaluated in nursing mothers.

8.4 Pediatric Use

Treatment of Primary Immunodeficiency

GAMUNEX was evaluated in 18 pediatric subjects (age range 0-16 years). Twenty-one percent of PI subjects (Study 100175) exposed to GAMUNEX were children. Pharmacokinetics, safety and efficacy were similar to those in adults with the exception that vomiting was more frequently reported in pediatrics (3 of 18 subjects). No pediatric-specific dose requirements were necessary to achieve serum IgG levels.

One subject, a 10-year-old boy, died suddenly from myocarditis 50 days after his second infusion of GAMUNEX. The death was judged to be unrelated to GAMUNEX.

Treatment of Idiopathic Thrombocytopenic Purpura

GAMUNEX was evaluated in 12 pediatric subjects with acute ITP. Twenty-five percent of the acute ITP subjects (Study 100176) exposed to GAMUNEX were children. Pharmacokinetics, safety and efficacy were similar to those in adults with the exception that fever was more frequently reported in pediatrics (6 of 12 subjects). No pediatric-specific dose requirements were necessary to achieve serum IgG levels.

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

The safety and effectiveness of GAMUNEX has not been established in pediatric subjects with CIDP.

8.5 Geriatric Use

Patients > 65 years of age may be at increased risk for developing certain adverse reactions such as thromboembolic events and acute renal failure. *(See Boxed Warning, Warnings and Precautions [5.2])* Clinical studies of GAMUNEX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Table 11: Clinical Studies of GAMUNEX® by Age Group

		Number of Subjects	
Clinical Study	Indication	< 65 years	≥ 65 years
100175	PI	78	9
100152	PI	18	0
100174	PI	20	0
10039	PI	19	0
100213	ITP	22	6
100176	ITP	44	4
10038	ITP	18	3
100538	CIDP	44	15

11 DESCRIPTION

GAMUNEX is a ready-to-use sterile solution of human immune globulin protein for intravenous administration. GAMUNEX consists of 9%–11% protein in 0.16–0.24 M glycine. Not less than 98% of the protein has the electrophoretic mobility of gamma globulin. GAMUNEX contains trace levels of fragments, IgA (average 0.046 mg/mL), and IgM. The distribution of IgG subclasses is similar to that found in normal serum. GAMUNEX doses of 1 g/kg correspond to a glycine dose of 0.15 g/kg. While toxic effects of glycine administration have been reported,[35] the doses and rates of administration were 3 – 4 fold greater than those for GAMUNEX. In another study, it was demonstrated that intravenous bolus doses of 0.44 g/kg glycine were not associated with serious adverse effects.[36] Caprylate is a saturated medium-chain (C8) fatty acid of plant origin. Medium chain fatty acids are considered to be essentially non-toxic. Human subjects receiving medium chain fatty acids parenterally have tolerated doses of 3.0 to 9.0 g/kg/day for periods of several months without adverse effects.[37] Residual caprylate concentrations in the final container are no more than 0.216 g/L (1.3 mmol/L).The measured buffer capacity is 35 mEq/L and the osmolality is 258 mOsmol/kg solvent, which is close to physiological osmolality (285-295 mOsmol/kg). The pH of GAMUNEX is 4.0 – 4.5. GAMUNEX contains no preservative and is latex-free.

GAMUNEX is made from large pools of human plasma by a combination of cold ethanol fractionation, caprylate precipitation and filtration, and anion-exchange chromatography. Isotonicity is achieved by the addition of glycine. GAMUNEX is incubated in the final container (at the low pH of 4.0 – 4.3), for a minimum of 21 days at 23° to 27°C. The product is intended for intravenous administration.

The capacity of the manufacturing process to remove and/or inactivate enveloped and non-enveloped viruses has been validated by laboratory spiking studies on a scaled down process model, using the following enveloped and non-enveloped viruses: human immunodeficiency virus, type I (HIV-1) as the relevant virus for HIV-1 and HIV–2; bovine viral diarrhea virus (BVDV) as a model for hepatitis C virus; pseudorabies virus (PRV) as a model for large DNA viruses (e.g., herpes viruses); Reo virus type 3 (Reo) as a model for non-enveloped viruses and for its resistance to physical and chemical inactivation; hepatitis A virus (HAV) as relevant non-enveloped virus, and porcine parvovirus (PPV) as a model for human parvovirus B19.

Overall virus reduction was calculated only from steps that were mechanistically independent from each other and truly additive. In addition, each step was verified to provide robust virus reduction across the production range for key operating parameters.

Table 12: Log_{10} Virus Reduction

Process Step	Log_{10} Virus Reduction					
	Enveloped Viruses			Non-enveloped Viruses		
	HIV	PRV	BVDV	Reo	HAV	PPV
Caprylate Precipitation/Depth Filtration	C/I [a]	C/I	2.7	≥ 3.5	≥ 3.6	4.0
Caprylate Incubation	≥ 4.5	≥ 4.6	≥ 4.5	NA [b]	NA	NA
Depth Filtration [d]	CAP [c]	CAP	CAP	≥ 4.3	≥ 2.0	3.3
Column Chromatography	≥ 3.0	≥ 3.3	4.0	≥ 4.0	≥ 1.4	4.2
Low pH Incubation (21 days)	≥ 6.5	≥ 4.3	≥ 5.1	NA	NA	NA
Global Reduction	≥ **14.0**	≥ **12.2**	≥ **16.3**	≥ **7.5**	≥ **5.0**	**8.2**

[a] C/I - Interference by caprylate precluded determination of virus reduction for this step. Although removal of viruses is likely to occur at the caprylate precipitation/depth filtration step, BVDV is the only enveloped virus for which reduction is claimed. The presence of caprylate prevents detection of other, less resistant enveloped viruses and therefore their removal cannot be assessed.

[b] Not Applicable – This step has no effect on non-enveloped viruses.

[c] CAP - The presence of caprylate in the process at this step prevents detection of enveloped viruses, and their removal cannot be assessed.

[d] Some mechanistic overlap occurs between depth filtration and other steps. Therefore, Talecris Biotherapeutics, Inc. has chosen to exclude this step from the global virus reduction calculations.

Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.[38-42]

Several of the individual production steps in the GAMUNEX manufacturing process have been shown to decrease TSE infectivity of that experimental model agent. TSE reduction steps include two depth filtrations (in sequence, a total of ≥ 6.6 logs). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Treatment of Primary Humoral Immunodeficiency

GAMUNEX supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacteria or their toxins. The mechanism of action in PI has not been fully elucidated.

Treatment of Idiopathic Thrombocytopenic Purpura

The mechanism of action of high doses of immunoglobulins in the treatment of Idiopathic Thrombocytopenic Purpura (ITP) has not been fully elucidated.

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

The precise mechanism of action in CIDP has not been fully elucidated.

12.3 Pharmacokinetics

Two randomized pharmacokinetic crossover trials were carried out with GAMUNEX in 38 subjects with Primary Humoral Immunodeficiencies given 3 infusions 3 or 4 weeks apart of test product at a dose of 100-600 mg/kg body weight per infusion. One trial compared the pharmacokinetic characteristics of GAMUNEX to GAMIMUNE N, 10% (study 100152), and the other trial compared the pharmacokinetics of GAMUNEX (10% strength) with a 5% concentration of this product (study 100174). The ratio of the geometric least square means for dose-normalized IgG peak levels of GAMUNEX and GAMIMUNE N, 10% was 0.996. The corresponding value for the dose-normalized area under the curve (AUC) of IgG levels was 0.990. The results of both PK parameters were within the pre-established limits of 0.080 and 1.25. Similar results were obtained in the comparison of GAMUNEX 10% to a 5% concentration of GAMUNEX.[31, 32]

The main pharmacokinetic parameters of GAMUNEX, measured as total IgG in study 100152 are displayed below:

Table 13: PK Parameters of GAMUNEX® and GAMIMUNE® N, 10% (Study 100152)

	GAMUNEX®				GAMIMUNE® N, 10%			
	N	Mean	SD	Median	N	Mean	SD	Median
Cmax (mg/mL)	17	19.04	3.06	19.71	17	19.31	4.17	19.30
Cmax-norm (kg/mL)	17	0.047	0.007	0.046	17	0.047	0.008	0.047
AUC(0-tn)[a] (mg*hr/mL)	17	6746.48	1348.13	6949.47	17	6854.17	1425.08	7119.86
AUC(0-tn)norm[a] (kg*hr/mL)	17	16.51	1.83	16.95	17	16.69	2.04	16.99
$T_{1/2}$[b] (days)	16	35.74	8.69	33.09	16	34.27	9.28	31.88

[a] Partial AUC: defined as pre-dose concentration to the last concentration common across both treatment periods in the same patient.

[b] only 15 subjects were valid for the analysis of $T_{1/2}$

The two pharmacokinetic trials with GAMUNEX show the IgG concentration/time curve follows a biphasic slope with a distribution phase of about 5 days characterized by a fall in serum IgG levels to about 65-75% of the peak levels achieved immediately post-infusion. This phase is followed by the elimination phase with a half-life of approximately 35 days.[31, 32] IgG trough levels were measured over nine months in the therapeutic equivalence trial (100175). Mean trough levels were 7.8 +/- 1.9 mg/mL for the GAMUNEX treatment group and 8.2 +/- 2.0 mg/mL for the GAMIMUNE N, 10% control group.[30]

14 CLINICAL STUDIES

14.1 Treatment of Primary Humoral Immunodeficiency

In a randomized, double-blind, parallel group clinical trial with 172 subjects with primary humoral immunodeficiencies (study 100175) GAMUNEX was demonstrated to be at least as efficacious as GAMIMUNE N, 10% in the prevention of any infection, i.e. validated plus clinically defined, non-validated infections of any organ system, during a nine month treatment period. Twenty six subjects were excluded from the Per Protocol analysis (2 due to non-compliance and 24 due to protocol violations). The endpoint was the proportion of subjects with at least one of the following validated infections: pneumonia, acute sinusitis and acute exacerbations of chronic sinusitis.

Table 14: Primary Endpoint Per Protocol Analysis (Study 100175)

	GAMUNEX® (n=73) No. of subjects with at least one infection	GAMIMUNE® N, 10% (n=73) No. of subjects with at least one infection	Mean Difference (90% confidence interval)	p-Value
Validated Infections	9 (12%)	17 (23%)	-0.117 (-0.220, -0.015)	0.06
Acute Sinusitis	4 (5%)	10 (14%)		
Exacerbation of Chronic Sinusitis	5 (7%)	6 (8%)		
Pneumonia	0 (0%)	2 (3%)		
Any Infection (Validated plus Clinically defined non-validated Infections)	56 (77%)	57 (78%)	-0.020 (-0.135, 0.096)	0.78

The annual rate of validated infections (Number of Infections/year/subject) was 0.18 in the group treated with GAMUNEX and 0.43 in the group treated with GAMIMUNE N, 10% (p=0.023). The annual rates for any infection (validated plus clinically-defined, non-validated infections of any organ system) were 2.88 and 3.38, respectively (p=0.300).[30, 43]

14.2 Treatment of Idiopathic Thrombocytopenic Purpura

A double-blind, randomized, parallel group clinical trial with 97 ITP subjects was carried out to prove the hypothesis that GAMUNEX was at least as effective as GAMIMUNE N, 10% in raising platelet counts from less than or equal to 20 $x10^9$/L to more than 50 $x10^9$/L within 7 days after treatment with 2 g/kg IGIV (study 100176). Twenty-four percent of the subjects were less than or equal to 16 years of age.

GAMUNEX was demonstrated to be at least as effective as GAMIMUNE N, 10% in the treatment of adults and children with acute or chronic ITP.[11]

Table 15: Platelet Response of Per Protocol Analysis (Study 100176)

	GAMUNEX® (n=39)	GAMIMUNE® N, 10% (n=42)	Mean Difference (90% confidence interval)
By Day 7	35 (90%)	35 (83%)	0.075 (-0.037, 0.186)
By Day 23	35 (90%)	36 (86%)	0.051 (-0.058, 0.160)
Sustained for 7 days	29 (74%)	25 (60%)	0.164 (0.003, 0.330)

A trial was conducted to evaluate the clinical response to rapid infusion of GAMUNEX in patients with ITP. The study involved 28 chronic ITP subjects, wherein the subjects received 1 g/kg GAMUNEX on three occasions for treatment of relapses. The infusion rate was randomly assigned to 0.08, 0.11, or 0.14 mL/kg/min (8, 11 or 14 mg/kg/min). Pre-medication with corticosteroids to alleviate infusion-related intolerability was not permitted. Pre-treatment with antihistamines, anti-pyretics and analgesics was permitted. The average dose was approximately 1 g/kg body weight at all three prescribed rates of infusion (0.08, 0.11 and 0.14 mL/kg/min). All patients were administered each of the three planned infusions except seven subjects. Based on 21 patients per treatment group, the a posteriori power to detect twice as many drug-related adverse events between groups was 23%. Of the seven subjects that did not complete the study, five did not require additional treatment, one withdrew because he refused to participate without concomitant medication (prednisone) and one experienced an adverse event (hives); however, this was at the lowest dose rate level (0.08 mL/kg/min).

14.3 Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

A multi-center, randomized, double-blind Placebo-controlled trial (study 100538, The Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified CIDP Efficacy or ICE study) was conducted with GAMUNEX.[44] This study included two separately randomized study periods to assess whether GAMUNEX was more effective than Placebo for the treatment of CIDP (assessed in the Efficacy Period for up to 24 weeks) and whether long-term administration of GAMUNEX could maintain long-term benefit (assessed in the 24 week Randomized Withdrawal Period).

In the Efficacy Period, there was a requirement for Rescue (crossover) to the alternate study drug if the subject did not improve and maintain this improvement until the end of the 24 week treatment period. Subjects entering the Rescue phase followed the same dosing and schedule as in the Efficacy period. Any subject who was Rescued (crossed over) and did not improve and maintain this improvement was withdrawn from the study.

Subjects who completed 24 weeks treatment in the Efficacy period or Rescue phase and responded to therapy were eligible for entry into a double-blind Randomized Withdrawal Period. Eligible subjects were re-randomized to GAMUNEX or Placebo. Any subject who relapsed was withdrawn from the study.

The Efficacy Period and the Rescue treatment started with a loading dose of 2 g/kg bw of GAMUNEX or equal volume of Placebo given over 2-4 consecutive days. All other infusions (including the first infusion of the Randomized Withdrawal Period) were given as maintenance doses of 1 g/kg bw (or equivalent volume of Placebo) every three weeks.

The Responder rates of the GAMUNEX and Placebo treatment groups was measured by the INCAT score. The INCAT (Inflammatory Neuropathy Cause and Treatment) scale is used to assess functional disability of both upper and lower extremities in demyelinating polyneuropathy. The INCAT scale has upper and lower extremity components (maximum of 5 points for upper (arm disability) and maximum of 5 points for lower (leg disability)) that add up to a maximum of 10-points (0 is normal and 10 is severely incapacitated).[45] At the start of the efficacy portion of the study, the INCAT scores were as follows: Upper Extremity mean was 2.2 $\pm$1.0, and median was 2.0 with a range of 0 to 5; Lower Extremity mean was 1.9 $\pm$0.9, and median was 2.0 with a range of 1 to 5; Total Overall Score mean was 4.2 $\pm$1.4, and median was 4.0 with a range of 2 to 9. A Responder was defined as a subject with at least 1-point improvement from baseline in the adjusted INCAT score that was maintained through 24 weeks.

Significantly more subjects with CIDP responded to GAMUNEX: 28 of 59 subjects (47.5%) responded to GAMUNEX compared with 13 of 58 subjects (22.4%) administered Placebo (25% difference; [95% CI: 7%-43%]; p=0.006). The study included both subjects who were IGIV naive and subjects who had previous IGIV experience. The outcome was influenced by the group of subjects who experienced prior therapy with IGIV, as shown by the outcomes table, below.

Time to relapse for the subset of 57 subjects who previously responded to GAMUNEX was evaluated: 31 were randomly reassigned to continue to receive GAMUNEX and 26 subjects were randomly reassigned to Placebo in the Randomized Withdrawal Period. Subjects who continued to receive GAMUNEX experienced a significantly longer time to relapse versus subjects treated with Placebo (p=0.011). The probability of relapse was 13% with GAMUNEX versus 45% with Placebo (hazard ratio, 0.19 [95% confidence interval, 0.05, 0.70]).

Table 16: Outcomes in Intent-to-Treat Population Efficacy Period

	GAMUNEX®		Placebo		
Efficacy Period	Responder	Non-Responder	Responder	Non-Responder	p-value[a]
All Subjects	28/59 (47.5%)	31/59 (52.5%)	13/58 (22.4%)	45/58 (77.6%)	0.006
IGIV - Naïve Subjects	17/39 (43.6%)	22/39 (56.4%)	13/46 (28.3%)	33/46 (71.7%)	0.174
IGIV - Experienced Subjects	11/20 (55.0%)	9/20 (45.0%)	0/12 (0%)	12/12 (100%)	0.002

[a] p-value based on Fisher's exact method

The following table shows outcomes for the Rescue Phase (which are supportive data):

Table 17: Outcomes in Rescue Phase

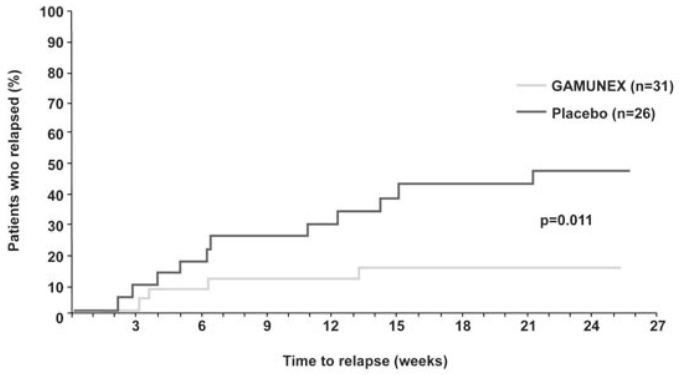
	GAMUNEX®		Placebo		
Rescue Phase	Success	Failure	Success	Failure	p-value[a]
All Subjects	25/45 (55.6%)	20/45 (44.4%)	6/23 (26.1%)	17/23 (73.9%)	0.038
IGIV - Naïve Subjects	19/33(57.6%)	14/33 (42.4%)	6/18 (33.3%)	12/18 (66.7%)	0.144
IGIV - Experienced Subjects	6/12 (50%)	6/12 (50%)	0/5 (0%)	5/5(100%)	0.102

[a] p-value based on Fisher's exact method

The following Kaplan-Meier curves show the outcomes for the Randomized Withdrawal Period:

Figure 1: Outcome for Randomized Withdrawal Period

Secondary Endpoint Randomized Withdrawal Period	Time to Relapse	p-value[a] p= 0.011



[a] p-value based on log-rank test

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16 HOW SUPPLIED/STORAGE AND HANDLING

GAMUNEX is supplied in single-use, tamper evident vials (shrink band) containing the labeled amount of functionally active IgG. The three larger vial size labels incorporate integrated hangers. The components used in the packaging for GAMUNEX are latex-free.

GAMUNEX is supplied in the following sizes:

NDC Number	Size	Grams Protein
13533-645-12	10 mL	1.0
13533-645-15	25 mL	2.5
13533-645-20	50 mL	5.0
13533-645-71	100 mL	10.0
13533-645-24	200 mL	20.0

GAMUNEX may be stored for 36 months at 2 - 8°C (36 - 46°F), AND product may be stored at temperatures not to exceed 25°C (77°F) for up to 6 months anytime during the 36 month shelf life, after which the product must be immediately used or discarded. Do not freeze. Do not use after expiration date.

17 PATIENT COUNSELING INFORMATION

(See Boxed Warning and Warnings and Precautions Sections)

Inform patients to immediately report the following to their physician:

- signs and symptoms of renal failures, such as decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath
- signs and symptoms of aseptic meningitis, such as headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting
- signs and symptoms of hemolysis, such as fatigue, increased heart rate, yellowing of the skin or eyes, and dark-colored urine
- signs and symptoms of TRALI, such as severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. TRALI typically occurs within 1 to 6 hours following transfusion.

Inform patients that GAMUNEX is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses, and, theoretically, the CJD agent). Inform patients that the risk GAMUNEX may transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing the donated plasma for certain virus infections and by inactivating and/or removing certain viruses during manufacturing.

Inform patients that administration of IgG may interfere with the response to live viral vaccines such as measles, mumps and rubella. Inform patients to notify their immunizing physician of therapy with GAMUNEX.

Manufactured by: Rx only

Talecris BIOTHERAPEUTICS

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14.5 National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 (09 August 2006)

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).						
ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*:	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
– Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome						
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*:	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
– Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia						
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – S*elect:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – S*elect*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death

ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin. ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis. ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Neuropathy: cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision	Harmful to others or self; life-threatening	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				or restraints indicated	consequences	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- – External ear
- – Middle ear

CARDIOVASCULAR
- – Cardiac/heart
- – Pericardium

DERMATOLOGY/SKIN
- – Face
- – Lip
- – Oral-gums
- – Scalp
- – Skin

GASTROINTESTINAL
- – Abdomen NOS
- – Anus
- – Dental/teeth/peridontal
- – Esophagus
- – Oral cavity
- – Peritoneum
- – Rectum
- – Stomach

GENERAL
- – Pain NOS
- – Tumor pain

HEPATOBILIARY/PANCREAS
- – Gallbladder
- – Liver

LYMPHATIC
- – Lymph node

MUSCULOSKELETAL
- – Back
- – Bone
- – Buttock
- – Extremity-limb
- – Intestine
- – Joint
- – Muscle
- – Neck
- – Phantom (pain associated with missing limb)

NEUROLOGY
- – Head/headache
- – Neuralgia/peripheral nerve

OCULAR
- – Eye

PULMONARY/UPPER RESPIRATORY
- – Chest wall
- – Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- – Larynx
- – Pleura
- – Sinus
- – Throat/pharynx/larynx

RENAL/GENITOURINARY
- – Bladder
- – Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- – Breast
- – Ovulatory
- – Pelvis
- – Penis
- – Perineum
- – Prostate
- – Scrotum
- – Testicle
- – Urethra
- – Uterus
- – Vagina

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select;* Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE (*continued*)
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL (*continued*)
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- CN I (olfactory)
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)

NEUROLOGY (*continued*)

NERVES:
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Lingual
- Lung thoracic
- Peripheral motor NOS
- Peripheral sensory NOS
- Recurrent laryngeal
- Sacral plexus
- Sciatic
- Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
ALSO CONSIDER: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

14.6 Additional Study Visits: Weeks 77 Through 105

	W77[1]	W79[1]	W81[1]	W83[1]	W85[1]	W87[1]	W89[1]	W91[1]	W93[1]	W95[1]	W97[1]	W99[1]	W101[1]	W103[1]	W105[1]
Physical Examination[2]		X		X		X		X		X		X		X	
Pregnancy Testing[3]		X		X		X		X		X		X		X	
Vital Sign Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Myozyme Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Research Immunophenotyping				X				X				X			
Lymphocyte Subpopulation Counts				X				X				X			
Functional T cell Assay (ELISPOT)				X				X				X			
Immunoglobulin Panel				X				X				X			
CBC with Differential		X		X		X		X		X		X		X	
Chemistry, CK and CK-MB		X		X		X		X		X		X		X	
Urinalysis		X		X		X		X		X		X		X	
Anti-rhGAA Antibody (IgG) Titers/Inhibitory Antibody Monitoring[4]		X		X		X		X		X		X		X	
ECG						X						X			
ECHO						X						X			
Pompe PEDI						X						X			
GMFM-66						X						X			
AIMS						X						X			

Additional Study Visits: Weeks 77 Through 105 (continued)

	W77[1]	W79[1]	W81[1]	W83[1]	W85[1]	W87[1]	W89[1]	W91[1]	W93[1]	W95[1]	W97[1]	W99[1]	W101[1]	W103[1]	W105[1]
Ventilator Use Monitoring	Continuous Monitoring														
Concomitant Medication Monitoring	Continuous Monitoring														
Concomitant Therapy Monitoring	Continuous Monitoring														
Adverse Event Monitoring	Continuous Monitoring														

[1] A visit window of ±2 weeks will be permitted for all additional study visits. For Myozyme infusions, the visit window is ±1 week.
[2] In addition to the scheduled physical examinations, brief, physical assessments should also be performed prior to the administration of any study medications (Myozyme) to ensure that the patient is clinically stable and can tolerate administration of these agents.
[3] Pregnancy testing will be performed monthly for female patients of childbearing potential, and patients with positive test results will be withdrawn from the study.
[4] If a patient becomes anti-rhGAA (IgG) positive during the course of the study, he/she will also be tested every 2 months for the presence of inhibitory antibodies to Myozyme.

Note: Appendix 14.6 provides a Schedule of Assessments for those patients who were <2 years of age at their W75 study visit and thus are required to continue following the protocol until they reach their second birthday (i.e., reach 2 years of age), at which time all EOS assessments should be performed for study completion. See Table 9-3 for further details.

Key: AIMS=Alberta Infantile Motor Scale; CBC=complete blood count; CK=creatine kinase; CK-MB=creatine kinase – myocardial band; ECG=electrocardiogram; ECHO; echocardiogram; ELISPOT=enzyme-linked immunosorbent spot [assay]; EOS=End-of-Study; GMFM-66=Gross Motor Function Measure-66; IgG=immunoglobulin G; IVIG=intravenous immunoglobulin; PEDI=Pediatric Evaluation and Disability Inventory; rhGAA=Recombinant human acid α-glucosidase; W=week