A single-center, randomized, double-blind, double-dummy, parallel-group study comparing oral sedation to intravenous sedation for ocular procedures.

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Principal Investigator: Manju Subramanian, MD
Phone: (617) 638-4455
E-mail: Manju.Subramanian@bmc.org

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1 List of Abbreviations

Abbreviation	Abbreviation Definition
AEs	Adverse events
BMC	Boston Medical Center
BMI	Body mass index
BUMC	Boston University Medical Campus
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRNA	Certified Registered Nurse Anesthetist
DMEK	Descemet membrane endothelial keratoplasty
DSEK	Descemet stripping endothelial keratopathy
FDA	Food and Drug Administration
IPS	Investigational Pharmacy Services
IRB	Institutional Review Board
ISAS	Iowa Satisfaction with Anesthesia Scale
IV	Intravenous
KPCO	Kaiser Permanente Colorado
ml	Milliliters
MPR	Minor procedure room
OR	Operating room
PI	Principal investigator
PO	By mouth
PPV	Pars plana vitrectomy
SAEs	Serious adverse events
SOC	Standard of care
UP	Unanticipated problem

2 Protocol Summary

Title:	A single-center, randomized, double-blind, double-dummy, parallel-group study comparing oral sedation to intravenous sedation for ocular procedures.
Population:	Male and female Boston Medical Center (BMC) patients 18 years or older, with a surgical plan within the cataracts, retina, cornea, and glaucoma sub-specialties services in the Ophthalmology Department
Interventions:	Oral medications • ACTIVE: Triazolam 0.125mg tablets, over-encapsulated for blinding • PLACEBO: Microcrystalline cellulose powder capsule to match triazolam • Dose: o BMI < 35: triazolam 0.125 mg/placebo (1 capsule) single dose by mouth approximately 30 min prior to procedure o BMI ≥ 35: triazolam 0.25 mg/placebo (2 capsules) single dose by mouth approximately 30 min prior to procedure Intravenous (IV) medications • ACTIVE: Midazolam 1mg/mL injection • PLACEBO: Sodium Chloride 0.9% • Dose: o BMI < 35: midazolam 1mg/placebo (1mL) single dose intravenously approximately 5 min prior to procedure o BMI ≥ 35: midazolam 2mg/placebo (2mL) single dose intravenously approximately 5 min prior to procedure
Objectives:	To determine if oral triazolam will provide a non-inferior level of patient satisfaction compared to IV midazolam when undergoing an ophthalmic surgical procedure.
Design/Methodology:	Surgical type 1: cataract procedures Surgical type 2: retina procedures Surgical type 3: cornea and ocular surface procedures Surgical type 4: glaucoma procedures Arm A: Oral triazolam with IV placebo to match midazolam Arm B: Oral placebo to match triazolam with IV midazolam Subjects will be randomized (1:1) to one of the two study arms listed above. On the day of surgery, the subject, anesthesiologist/CRNA, and surgeon will be blinded to the

	treatment assignment. The anesthesiologist/CRNA or pre-operative nurse will administer the blinded oral medication approximately 30 minutes before the procedure beings. The anesthesiologist/CRNA or pre-operative nurse will administer the blinded IV medication approximately 5 minutes before the procedure begins. At the completion of the procedure, the anesthesiologist/CRNA and the surgeon will complete a satisfaction survey. The subject will then return within 2 days for their first post-operative clinical visit and complete a satisfaction survey. Table 1 in the Appendix can be referenced for the schedule of study events.
Total Study Duration:	Approximately 1.5 years
Subject Participation Duration:	Subject participation length is variable based on sub-specialty procedures wait times and operating room availability: • Cataract: approximately 1-2 months • Retina: approximately 1-4 weeks • Cornea: approximately 1-2 months • Glaucoma: approximately 1-2 months

3 Background/Rationale & Purpose

3.1 Background Information

The Department of Ophthalmology at BMC has high demand for clinical visits and operating room procedures. As with most academic teaching institutions the operating room is shared with other surgical services, and accessibility for operating room space can be challenging. Most ocular procedures are short cases often requiring minimal anesthesia, some health care systems such as Kaiser Permanente are performing cataract procedures in a minor procedure room setting, either connected with an ambulatory surgery center or in a private office, under oral sedation with varying degrees of support from an Anesthesiologist. The Kaiser Permanente Colorado (KPCO) medical offices in Denver, Colorado have been performing cataract surgery in a minor procedure room (MPR) with oral sedation since 2006. They have published their 10-year experience reporting retrospectively on over 21,000 cases, stating that their model is safe and effective.[7]

Eye care services at BMC present some unique challenges, when compared to the KPCO experience. The patient population is vulnerable and has often had poor access to healthcare. Many patients have more advanced disease upon presentation. Many patients are also non-native English speakers or do not speak English at all. Additionally, as an academic teaching center where trainees assist in surgery, case times are longer than what may be experienced at KPCO.[7] Additionally, the KPCO experience evaluated only cataract surgery,[7] and did not report on other ocular surgical cases such as retina, cornea, and glaucoma procedures.

This study aims to compare the role of oral sedation (study group) to IV sedation (control group) in ocular procedures in a double-blind, double-dummy fashion. The primary outcome measured will be patient satisfaction. Secondary outcomes include surgeon satisfaction, anesthesiologist satisfaction, and safety.

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and BMC/BU Medical Campus Human Research Protection policies and procedures.

3.2 Rationale and Purpose

Midazolam is an FDA-approved intravenous medication commonly used as a sedative for ocular procedures conducted in the operating room. This study will compare the use of triazolam, an FDA-approved oral sedative for the same types of ocular procedures, a purpose which has not fully been investigated. The benzodiazepine triazolam was chosen as the oral medication due to its similarity to midazolam. The similarities between midazolam and triazolam include similar half-life, risks, and patient experience. [6,8] The medication doses were chosen from current SOC use based on weight.[6,8] The lower dose for both medications are used for patients with a BMI less than 35 and the higher dose is used for patients with a BMI greater than or equal to 35.

This is the first double-blind, prospective clinical trial that will compare IV and oral sedation for multiple ocular sub-specialty procedures. The procedures to be investigated are listed in Section 7.1 of this protocol, which include cataract, retina, cornea, and glaucoma surgical groups.

The purpose of this study is to demonstrate non-inferiority in patient satisfaction between the use of IV midazolam and oral triazolam. If the study shows that oral sedation is non-inferior to IV sedation, it may allow ocular procedures to be moved from the operating room into a procedure room setting in an ambulatory surgery center or office setting. If IV access is deemed unnecessary for some or all ocular procedures, then this may obviate the support of an anesthesiologist in the operating room. This will be beneficial for patients, as they will have a more desirable and uniform sedation experience with less risk of apnea that can be seen with IV sedation,[8] and since IV insertion will no longer be necessary, it will reduce the risk for IV-related side effects.[3] This benefits BMC by allowing more flexibility and availability of their operating rooms for more complex cases and high acuity patients undergoing general anesthesia, and could reduce anesthesiology-related costs if they are no longer needed to support eye cases.[1] Other surgical subspecialties that perform short cases currently under monitored anesthesia care could also consider this option in the future. This also has the potential to reduce health care costs in the long run for patients, third party payers, and BMC.[1]

4 Objectives

4.1 Study Objectives

The primary objective of this study is to compare patient satisfaction of oral triazolam to IV midazolam when administered for ocular procedures. The ocular procedures being investigated are for cataracts, retina, cornea, and glaucoma sub-specialties; a complete list of procedures included in this study can be found in Section 7.1 of this protocol. The primary endpoint will be measured by the patient satisfaction survey administered at the first post-operative clinic visit. The central hypothesis is that oral triazolam is non-inferior to IV midazolam when comparing patient satisfaction.

Secondary objectives include anesthesiologist/CRNA and surgeon satisfaction. These satisfaction means will be evaluated with an anesthesiologist/CRNA and a surgeon specific survey. Another secondary objective is to track the number of patients requiring additional anesthesia intervention during the procedure. And finally, we will track any intra-operative complications either related to the surgical procedure or the sedation, to assess patient safety.

4.2 Study Outcome Measures

Patient, anesthesiologist/CRNA, and surgeon satisfaction will be measured through personnel-specific satisfaction surveys. The anesthesiologist/CRNA and surgeon satisfaction surveys will be administered immediately after the completion of the surgical case. By doing so, this will create individualized case feedback and elicit more accurate responses. The patient satisfaction survey will be administered during the patient's first post-operative clinic visit, which occurs one or two days after the procedure. The day of the procedure was not chosen as the day to

administer the patient satisfaction survey because the patient will still be recovering from the effects of the sedation.

All surveys are a variation of the Iowa Satisfaction with Anesthesia Scale (ISAS), which has previously been used to measure patient satisfaction for cataract procedures by the KCPO.[5, 7] All satisfaction surveys are on a scale from 1 (least satisfied) to 6 (most satisfied). For each survey, every question's response will be independently scored from 1 to 6. All of the responses per survey will then be independently averaged to generate an individualized satisfaction score for the procedure. The individualized overall satisfaction score will be on the same 1-to-6 scale. Each sub-specialty surgical group of the study will be analyzed separately to determine non-inferiority between the two intervention groups.

Additional anesthesia intervention will be analyzed by calculating the number of subjects in each surgical group that receive additional anesthetic agents during the operative procedure after the initial sedation. Lastly, complication rates will be compared in order to determine the level of patient safety for each surgical procedure type.

Reference Section 12.0 for further statistical analysis explanations.

Reference Appendix Section 15.7 for patient and personnel-specific satisfaction surveys. The scoring guides can be found within Appendix Sections 15.4.3 and 15.4.4.

4.2.1 Primary Outcome Measures

The objective of this study is to assess the patient satisfaction of patients administered oral triazolam during ocular procedures.

4.2.2 Secondary Outcome Measures

The following secondary outcomes will also be measured:

1. Surgeon satisfaction score
2. Anesthesiologist/CRNA satisfaction score
3. Total additional anesthesia interventions
4. Total surgical complications

5 Study Design

This clinical trial is a prospective, single center, randomized, controlled study. A total of up to 400 subjects will be randomized, stratified by surgical groups (cataracts, retina, cornea, and glaucoma), in a 1:1 ratio with approximately 200 subjects randomized to receive the oral sedation and approximately 200 subjects randomized to receive the IV sedation. Subjects will be randomized based on the procedures outlined in Section 9.1.2. Subjects have an equal chance of being randomized to one of the following study arms:

- Arm A: Oral triazolam with placebo to match IV midazolam
- Arm B: Oral placebo to match triazolam with IV midazolam

The primary endpoint is the patient satisfaction score. This satisfaction score is defined as the overall average of the twelve scored survey questions, which will be completed at the patient's first pre-operative clinic visit. The secondary endpoints include anesthesiologist/CRNA and surgeon satisfaction during the surgical case. Furthermore, it will be analyzed if any additional anesthesia intervention was needed throughout the surgical procedure and if any complications occurred during the procedure.

Reference Appendix for a schematic of the study design in Section 15.2.

6 Potential Risks and Benefits

6.1 Risks

6.1.1 Risk Associated with Patient Comfort and Satsifaction

Oral sedation has not been extensively investigated as a substitute for IV sedation for SOC ocular surgical procedures. One risk with the transition of sedation routes is a change in the level of patient comfort and ultimately their satisfaction with the procedure. In order to maximize patient safety, comfort and satisfaction, the study will be conducted at the Moakley OR ambulatory surgery center with monitored anesthesia support as is currently done for all BMC SOC patients. The decision to administer additional IV medication will occur at the discretion of the attending surgeon, in consultation with the anesthesiologist or CRNA, based on their assessment of the patient's level of comfort during the procedure. This will allow the anesthesiologist/CRNA to administer additional medication when needed to ensure patient comfort.

6.1.2 Risks Associated with the Benzodiazepine Midazolam

Midazolam is utilized as sedation for SOC ocular surgical procedures in all age groups. If the patient is thought to be at a higher risk for developing any of the complications that could occur from midazolam, they will not be able to participate in the study.

Most Common Risks
The most common side effects of midazolam are difficulty with regular thoughts and functions, difficulty breathing, and an allergic reaction causing nausea or vomiting. Midazolam has shown a high incidence of partial or complete impairment for the next several hours after administration. The decision to allow patients to return to regular activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle is individualized.[8]

Other Adverse Events
Other reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported. These reported reactions could be due to inadequate or excessive dosing or improper administration.[8]

Debilitation and Comorbid Considerations
Adults with COPD have shown to be sensitive to the respiratory depressant effect of midazolam. Adults with chronic renal failure or congestive heart failure eliminate midazolam more slowly.[8]

Reference Appendix Section 15.4 for the complete midazolam package insert.

6.1.3 Risks Associated with the Benzodiazepine Triazolam

If the patient is thought to be at a higher risk for developing any of the complications that could occur from triazolam, they will not be able to participate in the study.

Most Common Risks
The most common risks of triazolam are difficulty with regular thoughts and functions, sleeping problems, or an allergic reaction causing difficulty breathing, nausea, vomiting, and airway closure. Triazolam has shown a high incidence of partial or complete impairment for the next several hours after administration. The decision to allow patients to return to regular activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle is individualized.[6]

Risk of Abnormal Thinking/Behavior
The emergence of new thinking/behavior abnormalities and sleep disturbances can be the consequence of an unrecognized psychiatric physical disorder. Some of these changes are characterized by decreased inhibition, like aggressiveness and extroversion that may seem excessive. Other behavioral changes include bizarre behavior, agitation, hallucinations, depersonalization, worsening depression, and suicidal thoughts. Some of these findings have been seen with administration of triazolam. The use of alcohol and other CNS depressants with triazolam can increase the risk of these behaviors.[6]

Triazolam Interaction with Medications that Inhibit Metabolism via Cytochrome P450 3A
Drugs that inhibits the initial step in triazolam metabolism may have an effect of the clearance of the medication.[6]

Reference Appendix Section 15.5 for the complete triazolam package insert.

6.1.4 Decreasing Associated Risk with Benzodiazepines Triazolam and Midazolam

In order to decrease any associated risk, the exclusion criteria will eliminate any patient with known problems when taking a benzodiazepine. Furthermore, there will be anesthesia intervention available from the time the study medications are administered to the time the patient is cleared for discharge. Any adverse or unanticipated events will be addressed immediately by the anesthesiologist and the medical team.

6.1.5 Risk of Intravenous Cannulation

Patients receiving oral sedition do not typically also receive an IV line. Complications associated with an IV line include infection, phlebitis and thrombophlebitis, emboli, pain, hematoma or hemorrhage, extravasation, arterial cannulation and needle stick injuries.[3] Only specific study personnel with the required medical training will be designated tasks associated with administering the oral and IV medications.

6.1.6 Risk Associated with Geriatric Patients taking a Benzodiazepine

Additionally, geriatric patients are at higher risk for the development of delirium after administration of benzodiazepines.[6,8] In order to reduce this risk, all patients 70 years of age or older will complete a delirium pre-screening questionnaire as demonstrated in Appendix Section 15.6. The questionnaire mimics pre-operative clearance screening already in place for geriatric patients as SOC.[4] If patients do not pass the delirium questionnaire pre-screen they will not be able to participate in the study. With these safe guards in place, patients with increased benzodiazepine vulnerability will be screened out of study participation, and those that pass the screening will be at a much lower risk of experiencing delirium.

Reference Appendix Section 15.6 for the complete delirium pre-screening questionnaire. The scoring guide can be found in the Screening and Consent CRF located in Appendix Section 15.3.1.

6.1.7 Risk Associated with Pregnancy and Nursing with a Benzodiazepine

Benzodiazepines, like triazolam and midazolam, can be harmful to a fetus.[6,8] In order to eliminate this risk all women who are pregnant or have a positive pregnancy test on the day of surgery will be ineligible to participate. It is SOC to administer urine pregnancy tests to all patients who are childbearing age, prior to their procedure.[4] Additionally, triazolam and midazolam are excreted in breast milk, which could pose a risk the infant.[6,8] For this reason, all women who are nursing will not be able to participate in this study.

6.1.8 Risk of Loss of Confidentiality

There is the unlikely possibility of breach of confidentiality. Confidentiality will be protected as stated in Section 11.1 of this protocol.

6.1.9 Unknown Risks

There may be unknown risks or discomforts involved. Study staff will update all subjects in a timely manner with any new information that may affect their health, welfare, or decision to participate in this study.

6.2 Potential Benefits

If the study shows that oral triazolam is non-inferior to IV midazolam, this may allow ocular surgeries to be performed under oral sedation and reduce the need for the use of IV medication. If IV access is deemed unnecessary for some or all ocular procedures, then this may obviate the need for anesthesiologist or CRNA support in the operating room, and patients may be monitored by a registered nurse instead. Potential benefits to patients are that oral sedation may provide a more desirable and uniform effect with less risk of nausea, vomiting and apnea than can be seen with IV sedation. This will also result in elimination of the risk for IV-related side effects, such as pain from extravasation of medication into the surrounding soft tissue as well as infection at the IV site.[3,8] Fasting on the day of surgery would not be required if oral sedation alone is used for ocular surgeries. Currently, patients are not allowed to eat or drink anything after midnight on the day of surgery[2], causing some of our patients fast for more than 12 hours. This will likely improve the patient's surgical experience by reducing the discomfort associated with fasting

Potential benefits to BMC include increasing the availability of existing OR spaces for more complex cases and higher acuity patients undergoing general anesthesia, increasing the efficiency and cost-effectiveness of ocular surgery cases, and possibly reducing anesthesiology-related costs if their role in supporting ocular surgery cases is reduced.[1] This will allow greater flexibility to surgeons and patients and help meet current demand for eye care services. This also has the potential to reduce health care costs in the long run for patients, third party payers, and BMC.[1]

6.3 Analysis of Risks in Relation to Benefits

Oral triazolam was selected due to its similar effects and risks to IV midazolam,[6,8] thus eliciting a similar procedural level of risk as noted above.

If the study demonstrates that oral triazolam is an acceptable substitution for IV midazolam, then patients undergoing eye surgery will have less exposure to IV-related risks, elimination of same day fasting, improved access to eye care, decreased procedural costs, and decreased wait time for elective eye surgery. The benefits of potentially changing the standard of sedation for eye surgery will outweigh the risks of participation in the study.

7 Study Subject Selection

7.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Inclusion criteria
    - Age 18 years or older
    - Ability to speak and read in English or Spanish or Haitian-Creole
    - Subjects able to consent for themselves
    - Outpatient surgical plan for any of the following procedures:
- Cataract Surgery
    - Cataracts
- Retina
    - PPV
    - PPV with cataracts, epiretinal membrane peel, pars plana lensectomy and/or endolaser
    - Silicone oil removal
- Cornea
    - DSEK
    - Cataracts with DSEK
    - DMEK
    - Cataracts with DMEK
    - Conjunctival and/or corneal lesion excisions
    - Pterygium
- Glaucoma
    - Ahmed valve
    - Ahmed valve with cataracts
    - Trabeculectomy
    - Trabeculectomy with cataracts
    - Baerveldt
    - Baerveldt with cataracts
    - Endocyclophotocoagulation
    - Endocyclophotocoagulation with cataracts
    - Istent
    - Istent with cataracts
    - Kahook
    - Kahook with cataracts
    - Cypass
    - Cypass with cataracts

7.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Exclusion criteria

- Surgical plan which includes general anesthesia
- Hypersensitivity or allergy to benzodiazepines
- Women who are pregnant, have a positive pregnancy test on the day of surgery, refuse a pregnancy test, or are nursing
- Previous delirium after anesthesia with a benzodiazepine
- Subjects 70 years of age or older who fail the delirium pre-screening questionnaire as shown in Appendix Section 15.6
- Currently experiencing the effects of drugs/alcohol
- Current oral/IV regimen of any medication inhibiting cytochrome P450 3A which includes ketoconazole, itraconazole, nefazodone, ritonavir, indinavir, nelavir, saquinavir, and lopinavir
- Subjects already enrolled in this study for the fellow eye
- Subjects enrolled in a clinical trial with an investigational drug within the past 3 months
- Failed anesthesia clearance to receive a benzodiazepine

8 Study Intervention

Arm A: Oral triazolam with IV placebo to match midazolam
Arm B: Oral placebo to match triazolam with IV midazolam

Oral medications
- ACTIVE: Triazolam 0.125mg tablets, over-encapsulated for blinding
- PLACEBO: Microcrystalline cellulose powder capsule to match triazolam
- Dose:
    - BMI < 35: 0.125 mg (1 capsule) single dose by mouth approximately 30 min prior to procedure
    - BMI ≥ 35: 0.25 mg (2 capsules) single dose by mouth approximately 30 min prior to procedure

Intravenous medications
- ACTIVE: Midazolam 1mg/mL injection
- PLACEBO: Sodium Chloride 0.9%
- Dose:
    - BMI < 35: 1mL (1mg) single dose intravenously approximately 5 min prior to procedure
    - BMI ≥ 35: 2mL (2mg) single dose intravenously approximately 5 min prior to procedure

IPS will be responsible for:
- Ordering the investigational products
- Receipt, storage, accountability, dispensing, destruction and record keeping for all investigational products
- Preparation of blinded doses
- Receipt and documentation of any unused doses

Reference Appendix Sections 15.4 for formulation, packaging, and labeling information about midazolam.

Reference Appendix Sections 15.5 for formulation, packaging, and labeling information about triazolam.

9 Study Procedures

The following study procedures will be performed for study-specific purposes:

- Review of inclusion/exclusion criteria for eligibility
- Informed consent
- Collection of demographic information
- Study specific medical and ophthalmic history
- Delirium pre-screening questionnaire for subjects 70 years of age or older
- Randomization: eligible subjects will be randomized to receive either Arm A or Arm B medications
- Dispense and administration of medication based on randomization
- Completion of survey by attending surgeon after surgical case
- Completion of survey by anesthesiologist/CRNA after surgical case
- Completion of survey by subject at the first post-operative clinical visit (+ 2 days of surgery)
- Collection of information regarding anesthesia intervention and surgical complications
- Collection of information regarding any AEs, SAEs, or UPs

The following procedures will be performed as SOC:

- Ophthalmic exam prior to surgery
- Planned outpatient surgical procedure
- Preoperative clearance
- Urine pregnancy test (if required)
- Ophthalmic exam approximately one day after surgery

9.1 Study Schedule

9.1.1 Screening and Consent

Cataract, retina, cornea, or glaucoma ophthalmology patients who are thought to be eligible for the study based on the eligibility criteria and review of their medical record by the investigator and/or designated study team member will be approached about study participation. The patient's provider (who could be an investigator) will introduce the study to the patient. The provider will alert the investigator (if they are not already an investigator) and/or the designated study team member to assist with enrollment. The following will then be completed by the investigator and/or the designated study team member:

- Review of study inclusion/exclusion criteria

- The consent form will be reviewed with the patient and all study related questions will be answered in a private exam room or consult room at a visit to the eye clinic or at the Moakley PACU on the day of the surgical procedure:
    - Both the patient and the investigator or the designated study team member conducting the consent form will sign
    - The patient will be sent home with a copy of the fully executed consent form
    - The patient will also be given the contact information of the principal investigator, clinical research coordinator, and 24-hour emergency number as listed below:

      Manju Subramanian, MD
      Principal Investigator
      Manju.Subramanian@bmc.org
      (617) 638-4555

      Marissa Fiorello
      Clinical Research Coordinator
      Marissa.Fiorello@bmc.org
      (617) 414-8848

      BMC Department of Ophthalmology
      Emergency after Hours
      (617) 638-8000, dial 0 for operator, and ask for on-call ophthalmologist

- Study-specific review of medical record and demographics
- Schedule pre-operative clearance appointment
- Schedule surgical procedure

Alternatively, patients who may not be getting their surgery for 2-3 months may be contacted by a letter with a follow-up phone call 1 month prior to their surgery date regarding participation in the study. The patient will be given the option to discuss study participation at their next SOC, pre-operative clinical visit, set-up a separate study participation discussion visit, or discuss participation on the day of their procedure. If desired, a consent form will be mailed to the patient to review at home. Depending on how the patient would like to proceed with their participation, consent will be obtained during the SOC clinical visit, the study participation visit, or on the day of surgery. If the research team is unable to contact the patient by telephone or in clinic at a SOC appointment prior to the day of surgery, the research team will approach them on the day of surgery upon their arrival to the hospital to explain and discuss participation in the study.

If a subject has provided written informed consent and is 70 years of age or older, a delirium screening questionnaire will be administered in clinic during a SOC visit, a visit set-up to discuss study participation, or on the day of the procedure. All subjects in this age group are required to pass the delirium screening questionnaire in order to continue with enrollment.

If a woman of child bearing potential has provided written informed consent, a urine pregnancy test will be ordered to be completed on the day of surgery.

9.1.2 Pre-Procedure and Randomization

For the pre-procedure and randomization procedures, the following will be completed:

- Study-specific review of inclusion/exclusion criteria
- Preoperative clearance confirmation: Approximately 1-2 weeks from enrollment for retina procedures, and 1-3 months from randomization for all other procedures
    - Before the scheduled day of surgery, the subject must complete their individualized preoperative clearance plan.
- Confirm surgical procedure date
- Randomization: After screening, subjects who meet eligibility criteria will be randomly assigned to Arm A or Arm B based on the randomization tables, generated by the statistician, stratified by type of surgical group using a blocking scheme with a block size of 6.
    - Each randomization spot will be assigned a randomization ID of four numbers. The first number will indicate the surgical group, while the last three numbers will be the randomization number. The randomization ID will be paired with the subject ID at the time of randomization.
    - The randomization records will be placed in sealed envelopes by the statistician to ensure that data collection is completed in a blinded fashion. When an eligible subject is enrolled and ready to be randomized, the study team will select the sealed envelope with the randomization ID written on the outside to be readily available in case of an emergency. IPS will have a copy of the unblinded randomization table in order to match the randomization ID with the appropriate treatment arm.

9.1.3 Follow-Up Study Visits

Day of Surgery: Within 30 days of preoperative clearance

On the scheduled day of surgery, the following will be completed:

- Confirmation of eligibility and pre-operative clearance
- Urine pregnancy test (if required)
- Administration of randomized oral Arm A or Arm B medication by the blinded anesthesiologist/CRNA or pre-operative nurse

    - This will occur approximately 30 minutes before the start of the subjects surgical procedure
- Administration of randomized intravenous Arm A or Arm B medication by the blinded anesthesiologist/CRNA or pre-operative nurse
    - This will occur approximately 5 minutes before the start of the subjects surgical procedure in the OR
- The surgical case will be completed as planned
    - The local anesthetic used during each case and the route of administration will be determined by the surgeon according to SOC, and the information recorded.
    - If the subject requires additional anesthetic, this can be administered at the surgeon's discretion and will be recorded for research purposes
- At the completion of the case, the anesthesiologist/CRNA and attending surgeon will be given a satisfaction survey to complete prior to moving onto the next case
- Assessment of possible AEs, SAEs, and UPs
- Information regarding additional anesthesia medication administration and case complications with be collected

Final Study Visit; Post-Operative Visit Day 1: Within 2 days after surgery

The following procedures will be completed at the post-operative day 1 visit

- Subject will complete a satisfaction survey independently
    - Subjects may ask a study team member for language clarification as needed
- Assessment of possible AEs, SAEs, and UPs
- Dispense $25 travel expense reimbursement
- Study participation is complete and the subject will complete the remainder of their post-operative appointments as scheduled for 1 week and 1 month from the day of their procedure

9.2 Early Termination Visit

The subject can be terminated early from the study if their surgical case is canceled and not rescheduled. Cancellation of a surgical case could be due to, but is not limited to, no longer requiring surgery, non-compliance with preoperative instructions, non-compliance with surgical procedure instructions, illness, death, etc.

9.3 Non-Study Visits (Unscheduled Visits)

At non-study visits a standard office ophthalmology exam will be completed.

9.4 Masking Procedure

All investigators, as well as other physicians, residents and study personnel who may come in contact with study subjects will be masked to treatment assignments during data collection. The statistician will create the blinded randomization tables which will be shared with IPS to ensure the correct study drug will be administered to each patient at each visit. Sealed envelopes will be made by the statistician which will have the randomization ID on the outside, and the treatment group on the inside. These envelopes will remain sealed during data collection, unless emergency unmasking is necessary.

Reference Appendix Section 15.1 for the schedule of events.

Reference Appendix Section 15.3 for the complete CRF used for all study visits which include the delirium questionnaire and satisfaction survey scoring guides.

Reference Appendix Section 15.6 for the Delirium Questionnaire.

Reference Appendix Section 15.7 for the patient and personnel-specific satisfaction surveys.

10 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

10.1 Definitions

The following definitions will be used in the assessment of safety:
Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Serious Adverse Event (SAE) is any adverse event that
(1) results in death;
(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem (UP) is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

10.2 Safety Review

Both the risks listed in Section 6.1 and unknown risks will be monitored throughout this minimal risk study. The PI will have overall responsibility for the study. The PI will review all AEs, SAEs, and UPs. During the review, the PI will complete the form designated in Appendix 15.8.1 in which the AE will be graded and the relatedness will be determined. All SAEs and UPs will be promptly reported to the BUMC IRB as designated in Section 10.3. The SAE Report demonstrated in Appendix Section 15.8.3 will be completed for all SAEs and UPs.

The PI will be notified within 1 week of any events determined an AE or SAE and 2 days of any event determined a UP. The PI will review all AEs/SAEs within 2 weeks and all UPs within 5 days. The PI will consult with the delegated safety monitor, Dr. Stephen Christiansen, as applicable after review of the event. After this review, any recommended changes will be made to the co-investigators in addition to the BUMC IRB as deemed necessary by the PI.

An interim safety review will take place every 3 to 4 months in which a statistician will consult with the delegated safety monitor to discuss any increased rates of AEs, SAEs, or UPs that are not typically seen in usual SOC. A report of this meeting will be created, as demonstrated in Appendix Section 15.8.4, and made available to the PI and co-investigators for their review. All findings determined from the interim safety review will be reported to the BUMC IRB based on Section 10.3 of the protocol.

A safety review will be conducted by the PI, co-investigators, and the safety monitor every month during the active recruitment phase of the study. During this review, any questions or concerns regarding dosage adjustment, optimization, and safety of oral or IV sedation will be addressed by co-investigators or other study personnel. None of the blinded investigators will be unblinded during this review. Investigators may be unblinded if a significant number of adverse events occur or the PI, in consultation with the safety monitor, chooses to do so because patient safety could not be appropriately discussed otherwise.

Reference Appendix Section 15.8 for all AE, SAE, and UP tracking and report examples.

10.3 Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus involving a fatal or life-threatening event will be reported to the IRB within 2 days of the investigator learning of the event.
- Unanticipated Problems occurring at BMC/BU Medical Campus not involving a fatal or life-threatening event will be reported to the IRB within 7 days of the investigator learning of the event.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.
- Reports from safety monitors with no recommended changes will be reported to the IRB at the time of continuing review.

10.4 Stopping Rules

A subject will be withdrawn from the study for any of the following reasons but are not limited to:

- SAE, or UP resulting from the administered study intervention such as an allergic reaction or breathing problems
- A positive pregnancy test
- Failure to complete the require pre-operative clearance
- Failure to comply with pre-operative instructions
- Emergency unmasking resulting from an SAE or UP

The study will be stopped if the safety monitor, Dr. Stephen Christiansen, in consultation with the statistician, determine that the number of AEs, SAE, and/or UPs exceed that of SOC ocular procedures.

10.5 Emergency Unmasking

Any member of the medical team caring for study subjects in emergency situations may determine that unmasking is necessary for clinical care.

If the subject's randomized intervention was unmasked, it will be included in the electronic medical record along with and explanation as to why unmasking was necessary for the subject's clinical care.

Investigational Pharmacy and the statistician will maintain the randomization table and if emergency unmasking is required will be available to unmask the treatment.

Events that are so substantial in treating the subject that the PI or co-investigator has deemed emergency unmasking necessary or have led to emergency unmasking or a subject, this will be reported as an SAE or UP to the BMC/BUMC IRB in accordance with Section 10.3

11 Data Handling and Record Keeping

11.1 Confidentiality

Only the clinical research staff in the Department of Ophthalmology will view patient identifiers for eligibility review. Once the patient is consented into the study they will be given a unique study-specific identification code. Subject identifiers and the study identification code will be linked in a secure password-protected master database located in a departmental networked server housed behind BMC's firewall. The master database will allow for subject re-identification, as necessary, for strict research-specific purposes. Only study personnel will have access to the master database.

Any paper records related to this study will be stored in locked cabinets or in a locked office. Any data that is analyzed by an outside source will not contain any identifiers. In the event that any information is stored on external storage, the data will be encrypted. Patient information will not be used in any other way than described in this protocol.

A description of this clinical trial will be available on http://clinicaltrials.gov, as required by U.S. Law. The website will not include information which can identify any of the subjects. At most, the website will include a summary of the results. The subject is able to search for the study at any time on the website by utilizing the ClinicalTrials.gov number shown on the first page of this protocol.

11.2 Source Documents

All source documents for this study will include the electronic medical record and the study-specific documents which includes the following:

- CRFs in Appendix Section 15.3
- Delirium questionnaires in Appendix Section 15.6

- Patient and personnel specific satisfaction surveys in Appendix Section 15.7
- AE, SAE, and UP tracking and reports in Appendix Section 15.8

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. Data may be transcribed legibly on CRFs supplied for each subject or directly inputted into an electronic system or any combination thereof.

11.3 Case Report Forms

The study case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, "N/D" will be written. If the item is not applicable to the individual case, "N/A" will be written. All entries will be printed legibly in blue or black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered above it. All such changes will be initialed and dated. There will be no erasures or white-out on CRFs. For clarification of illegible or uncertain entries, the clarification will be printed above the item, then initialed and dated.

See the Appendix Section 15.3 for the Screening and Consent, Pre-Procedure and Randomization, Day of Surgery, and Post-Operative Day 1 CRFs.

11.4 Study Records Retention

In accordance with BMC policy, the study records will be retained for at least seven years after completion of the study. Additionally, as required by the BMC/BUMC IRB, documentation of informed consent of subjects will be retained for at least three years after the study is closed. All of the required records may be preserved in hardcopy, electronic or other media form and must be accessible for inspection and copying by authorized individuals.

12 Statistical Plan

12.1 Study Hypotheses

12.1.1 Primary Objective: Patient Satisfaction

Formal hypothesis: Mean patient satisfaction score will be non-inferior when given oral triazolam in comparison to the mean patient satisfaction score of IV midazolam during ocular procedures.

Testable hypothesis: Patient satisfaction mean will be non-inferior when given oral triazolam in comparison to IV midazolam during all basic cataracts, retina, cornea, and glaucoma ocular procedures.

Null hypothesis: The null hypothesis is that the oral sedation group will have a primary endpoint mean equal to or less than that of the IV sedation group by the non-inferiority margin or more.

Alternate hypothesis: The alternative hypothesis is that the oral sedation group will have a primary endpoint mean higher than the IV sedation group rate minus the non-inferiority margin. Specifically:

$$H0: \mu_O < \mu_{IV} - \delta$$
$$HA: \mu_O \geq \mu_{IV} - \delta$$

Where μ_O is the true mean satisfaction score for the oral sedation, μ_{IV} is the true mean satisfaction score for the IV sedation arm, and δ is the non-inferiority margin.

12.1.2 First Secondary Objective: Surgeon Satisfaction

Formal hypothesis: Mean surgeon satisfaction score for oral triazolam will not be statistically significant in comparison to mean surgeon satisfaction score for IV midazolam during ocular procedures.

Testable hypothesis: Mean surgeon satisfaction score for oral triazolam will not be statistically significant in comparison to mean surgeon satisfaction score for IV midazolam during all cataracts, retina, cornea, and glaucoma ocular procedures.

Null hypothesis: Mean surgeon satisfaction score for oral triazolam will be statistically significant in comparison to mean surgeon satisfaction score for IV midazolam during all cataracts, retina, cornea, and glaucoma ocular procedures.

Alternate hypothesis: Mean surgeon satisfaction score for oral triazolam will not be statistically significant in comparison to mean surgeon satisfaction score for IV midazolam during all cataracts, retina, cornea, and glaucoma ocular procedures.

12.1.3 Second Secondary Obejctive: Anesthesiologist/CRNA Satisfaction

Formal hypothesis: Mean anesthesiologist/CRNA satisfaction score for oral triazolam will not be statistically significant in comparison to mean anesthesiologist/CRNA satisfaction score for IV midazolam during ocular procedures.

Testable hypothesis: Mean anesthesiologist/CRNA satisfaction score for oral triazolam will not be statistically significant in comparison to mean anesthesiologist/CRNA satisfaction score for IV midazolam during all cataracts, retina, cornea, and glaucoma ocular procedures.

Null hypothesis: Mean anesthesiologist/CRNA satisfaction score for oral triazolam will be statistically significant in comparison to mean anesthesiologist/CRNA satisfaction score for IV midazolam during all cataracts, retina, cornea, and glaucoma ocular procedures.

Alternate hypothesis: Mean anesthesiologist/CRNA satisfaction score for oral triazolam will not be statistically significant in comparison to mean anesthesiologist/CRNA satisfaction score for IV midazolam during all cataracts, retina, cornea, and glaucoma ocular procedures.

12.1.4 Third Secondary Objective: Additional Anesthesia Intervention

Formal hypothesis: The total additional anesthesia interventions for oral triazolam will not be statistically significant in comparison to total additional anesthesia interventions for IV midazolam during ocular procedures.

Testable hypothesis: The total additional anesthesia interventions for oral triazolam will not be statistically significant in comparison to total additional anesthesia interventions for IV midazolam during all cataracts, retina, cornea, and glaucoma ocular procedures.

Null hypothesis: The total additional anesthesia interventions for oral triazolam will be statistically significant in comparison to total additional anesthesia interventions for IV midazolam during all cataracts, retina, cornea, and glaucoma ocular procedures.

Alternate hypothesis: The total additional anesthesia interventions for oral triazolam will not be statistically significant in comparison to total additional anesthesia interventions for IV midazolam during all cataracts, retina, cornea, and glaucoma ocular procedures.

12.1.5 Fourth Secondary Objective: Surgical Complication Rates

Formal hypothesis: The total surgical complications for oral triazolam will not be statistically significant in comparison to total surgical complications for IV midazolam during ocular procedures.

Testable hypothesis: The total surgical complications for oral triazolam will not be statistically significant in comparison to total surgical complications for IV midazolam during all cataracts, retina, cornea, and glaucoma ocular procedures.

Null hypothesis: The total surgical complications for oral triazolam will be statistically significant in comparison to total surgical complications for IV midazolam during all cataracts, retina, cornea, and glaucoma ocular procedures.

Alternate hypothesis: The total surgical complications for oral triazolam will not be statistically significant in comparison to total surgical complications for IV midazolam during all cataracts, retina, cornea, and glaucoma ocular procedures.

12.2 Sample Size Determination

A mean standard care satisfaction score of 5.5 with a standard deviation of 1 for the intravenous-first "standard" treatment, values consistent with prior literature.[1] The following assumptions are made in the sample size calculation

- True mean patient satisfaction is 5.5 in both treatment groups
- Power is 90%.
- 0.5 is the absolute non-inferiority margin
- Standard deviation of the score 0.75
- 5% One-sided type I error

Rejection of the null hypothesis will signify that the oral sedation is not inferior to the IV sedation with regards to the patient satisfaction score.

A total of 80 subjects (40 in the oral sedation group and 40 in the IV sedation group) will have 90% power to reject the above null hypothesis in favor of the alternative under the stated assumptions. To account for possible missing data (expected to be approximately 20%), a total of 100 subjects will need to be randomized.

Since each study intervention group will require a total of 50 subjects within each study arm, this means each surgical group will have a total of 100 subjects. There are four study surgical outcome groups in this study, totaling up to 400 subjects for the entire project.

400 subjects over the projected 11 months of recruitment is a feasible number because the subjects' active length of study participation is over the course of 2-3 days. Additionally, the ophthalmology department operates on over 2000 cases per year, 58% of which are cataract surgery cases. Recruitment rates in the different surgical groups will vary, as it is anticipated that since cataract surgery has the highest case volume, the cataract group will complete recruitment prior to the other surgical groups of the study. In terms of research support staffing, there will also be one study team member whose only responsibility is to consent and maintain this study, with a possible additional part time volunteer. They will also have the assistance of the rest of the study team as needed.

12.3 Statistical Methods

12.3.1 Margin on Non-Inferiority

Non-inferiority margin is a value that defines the magnitude of the amount that is not of practical importance. In our pilot study we found the mean patient satisfaction with IV sedation to be 5.5. This corresponds to a score between "Very Satisfied" and "Satisfied". A non-inferiority margin

of 0.5, will assure that, if non-inferiority is proven, the mean patient satisfaction with oral sedation will correspond to scores corresponding to satisfied or higher. We determined a 0.5 margin to be considered clinically similar enough to declare non-inferiority because it allows for expected patient satisfaction variability, and demonstrates ample justification for providers to offer oral sedation as a safe alternative.

12.3.2 Primary Outcome

Patient satisfaction scores. The mean satisfaction score of the oral sedation study group will be analyzed and compared to the mean satisfaction score of the IV sedation study group within surgical types using a t-test for non-inferiority in order to determine non-inferiority with a non-inferiority margin of 0.5.

As a sensitivity analysis, an ANCOVA model will be fit to the data adjusting for factors that are out of balance following randomization. The mean difference between the adjusted means will be calculated. If the lower bound of the 90% two-sided Confidence Interval of mean difference is higher than -0.5, the oral sedation will be deemed non-inferior to IV sedation.

12.3.3 Secondary Outcomes

Surgeon satisfaction score, and anesthesiologist/CRNA satisfaction score will be independently analyzed. Summary statistics including, means, standard deviations along with points estimates of the mean difference between the two groups and 90% Confidence Intervals.

Additional anesthesia intervention will be using summary statistics including, counts and proportions along with point's estimates of the proportion difference between the two groups and 90% Confidence Intervals.

Surgical complications will be using summary statistics including, counts and proportions along with point's estimates of the proportion difference between the two groups and 90% Confidence Intervals.

Each surgical procedure type is anticipated to complete enrollment at varying time points throughout the entire study. Once one surgical group type has completed recruitment, it will be closed and data and statistical analysis will begin, even if it occurs prior to completion of recruitment of the other surgical study groups. By doing so, the study team will be able to provide to BMC with results by surgical case type in a timely fashion, which may allow for operational decisions regarding OR space allocation to be made.

The primary analysis will be analyzing subjects according to the group they were randomized (Intention To Treat (ITT)). In secondary analyses, subjects will be analyzed according to the treatment they received (Per Protocol (PP)).

13 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the BMC and Boston University Medical Campus IRB, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

14 Literature References

1. Ambulatory Surgery Center Association. Commercial Insurance Costs Savings in Ambulatory Surgery Center 2016; Available from: http://www.advancingsurgicalcare.com/reducinghealthcarecosts/costsavings/healthcarebluebookstudy. Accessed August 13, 2017.
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3. Campbell J. Intravenous cannulation: potential complications. Prof. Nurse. 1997 May; 12 (8 Suppl): S10-3. Review.
4. Committee on Standards and Practice Parameters, Apfelbaum JL, Connis RT, Nickinovich DG; American Society of Anesthesiologists Task Force on Preanesthesia Evaluation, Pasternak LR, Arens JF, Caplan RA, Connis RT, Fleisher LA, Flowerdew R, Gold BS, Mayhew JF, Nickinovich DG, Rice LJ, Roizen MF, Twersky RS. Practice advisory for preanesthesia evaluation: an updated report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation. Anesthesiology. 2012 Mar; 116(3):522-38. doi: 10.1097/ALN.0b013e31823c1067.
5. Fung D, Cohen M, Stewart S, Davies A. Can the Iowa Satisfaction with Anesthesia Scale be used to measure patient satisfaction with cataract care under topical local anesthesia and monitored sedation at a community hospital? Anesthesia & Analgesia. 2005;100(6):1637–1643.
6. Greenstone LLC Browser [Internet]. Peapack (NJ): Greenstone LLC Product Database; 2017- Triazolam Tablets, USP CIV; [cited 2017 Jul 31]; [about 16 p.]. Available from: http://labeling.greenstonellc.com/showlabeling.aspx?id=917
7. Ianchulev T, Litoff D, Ellinger D, Stiverson K, Packer M. Office-Based Cataract Surgery: Population Health Outcomes Study of More than 21 000 Cases in the United States. Ophthalmology. 2016 Apr;123(4):723-8. doi: 10.1016/j.ophtha.2015.12.020. Epub 2016 Jan 22.
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15 Appendix

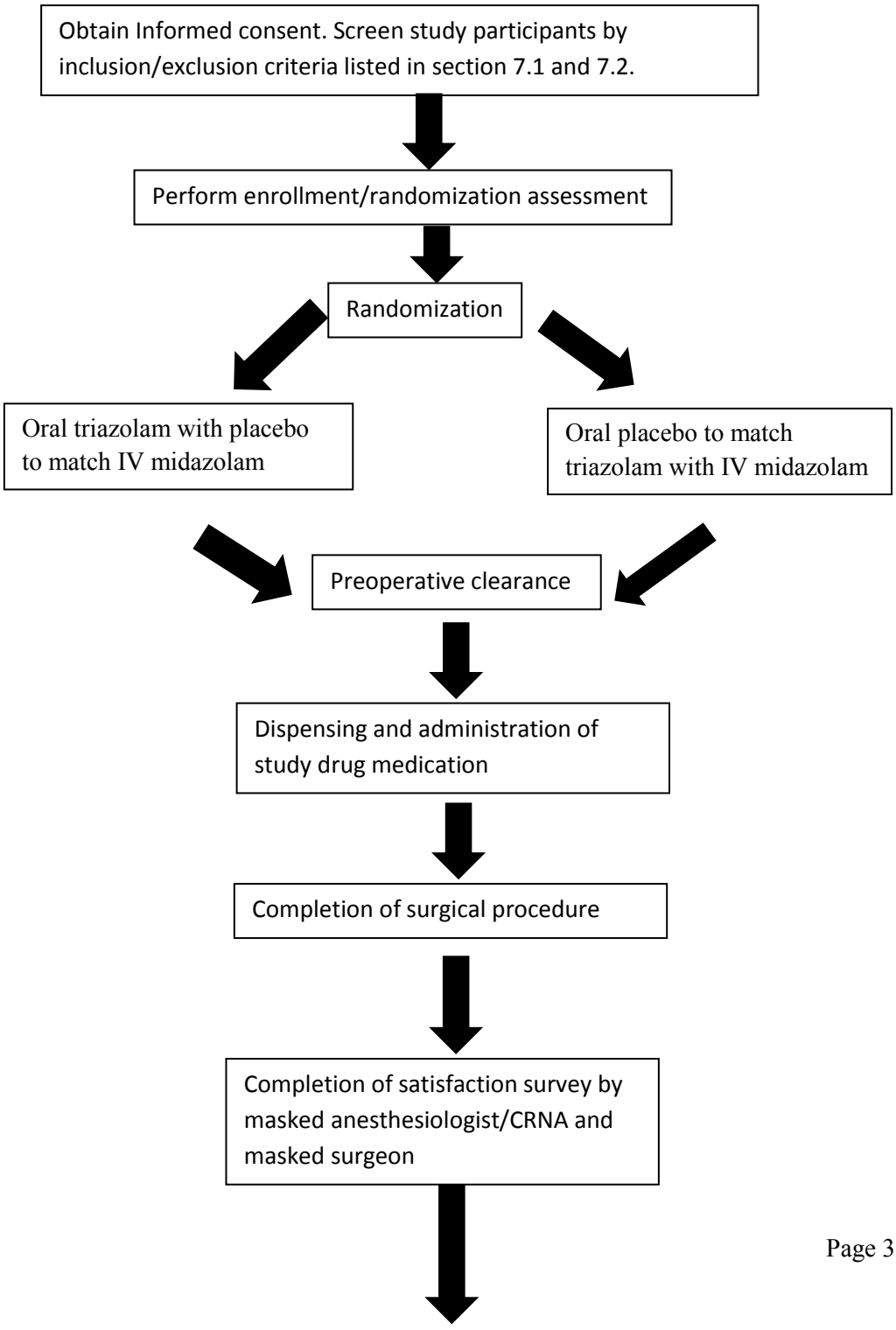
15.1 Schedule of Events: Source documents include medical records, satisfaction surveys, and all other information necessary to reconstruct and evaluate the clinical trial. See table 1 below for schedule of events.

Table 1: Schedule of Events. This table demonstrates the procedures to be completed at each study visit.

Procedures	Screening and Consent	Pre-Procedure and Randomization	Day of Surgery	1 day Post-Operative Clinic Visit
Informed consent	X			
Study specific review of medical/ophthalmic history	X			
Study specific review of demographics	X			
Review of inclusion/exclusion criteria	X	X	X	
Pregnancy Test (if required)			X	
Delirium Pre-Screening Questionnaire	X			
Randomization		X		
Schedule/Confirm Pre-operative Clearance	X	X	X	
Schedule/Confirm Surgical Procedure	X	X		
Coordinate with IPS	X	X	X	
Medication is dispensed			X	
Medication is administered to subject			X	
Assessment and documentation of additional anesthesia interventions			X	
Assessment and documentation of intraoperative complications			X	
Completion of survey by anesthesiologist			X	
Completion of survey by attending surgeon			X	
Completion of survey by subject				X

Assessment of possible AEs and/or SAEs			X	X

15.2 Schematic of Study Design



Completion of satisfaction survey by participant

15.3 Case Report Forms (CR

15.3.1 Screening and

SCREENING AND CONSENT CHECKLIST

- □ Review inclusion/exclusion criteria eligibility
- □ Sign consent form
- □ Administer delirium questionnaire for subject over 70 years of age or older
- □ Confirm eligibility based on delirium questionnaire results (if required)
- □ Collection of demographic information
- □ Collection medical/ophthalmic history
- □ Schedule pre-operative clearance
- □ Schedule surgical procedure
- □ Discharge with surgical procedure instructions

ELIGIBILITY CRITERIA REVIEW

INCLUSION CRITERIA ***Must be "yes"***	**Yes**	**No**	**Notes**
1. Age 18 years or older	☐	☐	
2. Ability to speak and read in English or Spanish or Haitian Creole	☐	☐	
3. Subjects able to consent for themselves	☐	☐	

4. Outpatient surgical plan for any of the following procedures:
• Cataract Surgery
  o Cataracts
• Retina
  o Pars plana vitrectomy (PPV)
  o PPV with cataracts, epiretinal membrane peel, pars plana lensectomy and/or endolaser
  o Silicone oil removal
• Cornea
  o DSEK
  o Cataracts with DSEK
  o DMEK
  o Cataracts with DMEK
  o Conjunctival and/or corneal lesion excisions
  o Pterygium
• Glaucoma
  o Ahmed valve
  o Ahmed valve with cataracts
  o Trabeculectomy
  o Trabeculectomy with cataracts
  o Baerveldt
  o Baerveldt with cataracts
  o Endocyclophotocoagulation
  o Endocyclophotocoagulation with cataracts
  o Istent
  o Istent with cataracts
  o Kahook
  o Kahook with cataracts
  o Cypass
  o Cypass with cataracts
	☐	☐	Category: ☐ cataracts
			☐ retina
			☐ cornea
			☐ glaucoma
			
			Name of Procedure: _____
			_____
			_____

EXCLUSION CRITERIA *Must be "no"*	**Yes**	**No**	**N/A at this time**	**Notes**
1. Surgical plan which includes general anesthesia	☐	☐	☐	
2. Hypersensitivity or allergy to benzodiazepines	☐	☐	☐	
3. Women who are pregnant, have a positive pregnancy test on the day of surgery, refuse a pregnancy test, or are nursing	☐	☐	☐	
4. Previous delirium after anesthesia with a benzodiazepine	☐	☐	☐	
5. Subject is 70 years of age or older and failed the delirium pre-screening questionnaire	☐	☐	☐	
6. Currently experiencing the effects of drugs/alcohol	☐	☐	☐	
7. Current oral/IV regimen of any medication inhibiting cytochrome P450 3A which includes ketoconazole, itraconazole, nefazodone, ritonavir, indinavir, nelavir, saquinavir, and lopinavir	☐	☐	☐	
8. Subjects already enrolled in this study for the fellow eye	☐	☐	☐	
9. Subjects enrolled in a clinical trial with an investigational drug within the past 3 months	☐	☐	☐	
10. Failed anesthesia clearance to receive a benzodiazepine	☐	☐	☐	

This subject is:

☐ **Eligible for participation** ☐ **Ineligible for participation**

Signed by study team member who is (1) qualified to assess eligibility and (2) delegated this study task by the PI

Signature:	**Date:**
Printed Name:	

INFORMED CONSENT

Confirm all of the following Occurred During the Consent Process	Yes	No	Notes
The study was explained and the consent form was reviewed with the participant.	☐	☐	
All of the participant's questions were answered and all the consent elements, such as purpose, procedures, and risks were reviewed.	☐	☐	
The participant was given sufficient time to consider participation.	☐	☐	
The participant agreed to participate in the study and personally signed and dated the consent form.	☐	☐	
The consent form was signed and dated by a designated member of the study team.	☐	☐	
The consent process was completed *prior to the start of research procedures.*	☐	☐	
Date and time informed consent form signed:	Date: _____ Time (24 hour clock): ___ ___ : ___ ___		
Version of ICF signed (e.g., V1, V2)			
Was subject given a copy of the signed consent form with contact information?	☐ Yes ☐ No – add comment below		
Comments: _____ _____			
Signature of person completing above fields **Signature: _____ Date: _____**			

DELIRIUM QUESTIONNAIRE SCORING

For each question select the response(s) as it pertains to each question. For each response(s) follow the table across to determine the point equivalent. Total each section point equivalents at the bottom of the table. On page 8 enter each section point equivalents and add them together, giving you the final delirium pre-screening questionnaire score to determine eligibility. All scores from 0-9 will be ELIGIBLE for participation. All scores of 10 or greater will be INELIGIBLE for participation.

☐ N/A Patient is < 70 years of age, delirium questionnaire and corresponding score sheet does not need to be completed

Subject Responses Scoring Sheet Part 1		
Question	Response	Point Equivalent
1. Have you ever experienced delirium after surgery or a procedure?	☐ a. Yes	☐ 10 points
	☐ b. No	☐ 0 points
Part 1 Point Total *Select only one*	☐ 0 points ☐ 10 points	
Subject Responses Scoring Sheet Part 2		
Question	Response	Point Equivalent
2. Have you ever been diagnosed with dementia?	☐ a. Yes	☐ 6 points
	☐ b. No	☐ 0 points
3. Have you ever been diagnosed with any of the following? Check all that apply. *If this was not answered, write "N/A".*	☐ a. Depression	☐ 1 point
	☐ b. Liver failure	☐ 1 point
	☐ c. Hypotension	☐ 1 point
	☐ d. Stroke	☐ 1 point
	☐ e. Alcoholism/substance abuse	☐ 1 point
	☐ f. Kidney failure	☐ 1 point
4. Are you able to complete you daily activities independently? *If this was not answered, write "N/A".*	☐ a. Yes	☐ 0 points
	☐ b. No	☐ 1 points
5. Are you able to get everywhere you need to by yourself during the day? *If this was not answered, write "N/A".*	☐ a. Yes	☐ 0 points
	☐ b. No	☐ 1 points
Part 2 Point Total *Select only one response or select 0 points if no questions were answered in this section*	☐ 0 points ☐ 1 point ☐ 2 points ☐ 3 points ☐ 4 points ☐ 5 points ☐ 6 points ☐ 7 points	☐ 8 points ☐ 9 points ☐ 10 points ☐ 11 points ☐ 12 points ☐ 13 points ☐ 14 points

Research Staff Scoring Sheet		
Question	Response	Point Equivalent
1. Does the patient take any of the following medication? *If patient does not take any medications, please mark "0 points"*	☐ Opioids *(1-2 medications selected)*	☐ 1 point
	☐ Opioids *(3 or more medications selected)*	☐ 6 points
	☐ Anticonvulsants *(1-2 medications selected)*	☐ 1 point
	☐ Anticonvulsants *(3 or more medications selected)*	☐ 6 points
	☐ Benzodiazepines *(1-2 medications selected)*	☐ 1 point
	☐ Benzodiazepines *(3 or more medications selected)*	☐ 6 points
	☐ Anticholinergics *(1-2 medications selected)*	☐ 1 point
	☐ Anticholinergics *(3 or more medications selected)*	☐ 6 points
	☐ Antipsychotics *(1-2 medications selected)*	☐ 1 point
	☐ Antipsychotics *(3 or more medications)*	☐ 6 points

Point Total *Select only one response or select 0 points if no questions were answered in this section*	☐ 0 points ☐ 1 ☐ 6 ☐ 11 ☐ 16 ☐ 21 ☐ 26 ☐ 2 ☐ 7 ☐ 12 ☐ 17 ☐ 22 ☐ 27 ☐ 3 ☐ 8 ☐ 13 ☐ 18 ☐ 23 ☐ 28 ☐ 4 ☐ 9 ☐ 14 ☐ 19 ☐ 24 ☐ 29 ☐ 5 ☐ 10 ☐ 15 ☐ 20 ☐ 25 ☐ 30

Eligibility Assessment Scoring Sheet	
Section	Point Total
Subject Part 1 Response Total *Enter Response from page 5*	
Subject Part 2 Response Total *Enter Response from page 5*	
Doctor Response Total *Enter Response from page 6*	
Overall Delirium Questionnaire Total *Total of all three sections listed above*	
Eligibility Assessment	☐ Score of 0-9 → Patient is ELIGIBLE for study. ☐ Score of 10+ → Patient is INELIGIBLE for study.

This subject is:

☐ **Eligible for participation** ☐ **Ineligible for participation**

Signed by study team member who is (1) qualified to assess eligibility and (2) delegated this study task by the PI

Signature:	**Date: ____/____/_____**
Printed Name:	

DEMOGRAPHIC INFORMATION

Date of Birth:		**Age (18 years or older):**	
Sex:	☐ Male ☐ Female ☐ Unknown ☐ Undifferentiated	*If female, is subject of child bearing potential?* ☐ Yes ☐ No	
Is the subject of Hispanic/Latino descent?	☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Not reported ☐ Unknown		
Race (check all that apply):	☐ American Indian or Alaskan Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Declined/ Not Available ☐ Other: _____		
Comments: _____ _____			
Signature of person completing above fields **Signature:** _____ **Date:** _____			

PATIENT VITALS

Measured?	☐ Measured → *Complete Table A.* ☐ Not measured → *Complete Table B.*
Table A *Patient Vitals were Measured*	
Date vitals were taken:	Date: _____
Height	_____ feet _____ inches
Weight	_____ lbs.
BMI	
Do vitals need to be re-measured? *Vitals must be re-measured if they were not measured when consented in clinic, at an in-person pre-operative appointment, or at another appointment within the past month*	☐ Yes, they will be re-measured at: ☐ Pre-operative appointment ☐ On the day of surgery ☐ Other: _____ ☐ No → Vitals can be used for medication dosing
Table B *Patient Vitals were Not Measured*	
When will vitals be measured?	☐ At a pre-operative appointment ☐ On the day of surgery ☐ Other: _____
Comments: _____ _____	
Signature of person completing above fields **Signature:** _____ **Date:** _____	

MEDICAL/OPHTHALMIC HISTORY

Has the subject experienced any previous illnesses, or surgeries, or is the subject currently experiencing any illnesses, allergies, or chronic conditions or diseases?	☐ Yes → *Complete the medical and ophthalmic condition tables below.* ☐ No → *Form is complete.*
Systemic hypertension	☐ Yes → *Add to table below.* ☐ No
Diabetes mellitus	☐ Yes → *Add to table below.* ☐ No
Hyperlipidemia	☐ Yes → *Add to table below.* ☐ No
Tobacco use	☐ Yes → *Add to table below.* ☐ No
Asthma/Bronchitis/COPD	☐ Yes → *Add to table below.* ☐ No
Hypercholesterolemia	☐ Yes → *Add to table below.* ☐ No
Heart disease	☐ Yes → *Add to table below.* ☐ No

Comments:

_____

_____

Signature of person completing above fields

Signature: _____ **Date:** _____

MEDICAL CONDITIONS

Medical Condition/Event	Onset Date	Ongoing or Resolved	End/Resolution Date
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	

Comments:

_____

_____

Signature of person completing above fields

Signature: _____ **Date:** _____

OPHTHALMIC CONDITIONS

Ophthalmic Condition/Event	Onset Date	Ongoing or Resolved	End/Resolution Date
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	
		□ Ongoing □ Resolved	

Comments:

_____

_____

Signature of person completing above fields

Signature: _____ **Date:** _____

SCHEDULE OF PRE-OPERATIVE CLEARANCE

Date of pre-operative clearance: *If not scheduled yet, write "will be scheduled"*	Date: _____
Type of surgical pre-operative clearance	□ Over the phone □ In-person
Comments: _____ _____	
Signature of person completing above fields **Signature: _____ Date: _____**	

SCHEDULE OF SURGICAL PROCEDURE

Date of surgical procedure: *If not scheduled yet, write "will be scheduled"*	Date: _____
Name of surgical procedure:	Category: ☐ retina ☐ cataract ☐ glaucoma ☐ cornea Name of Procedure: _____ _____
Name of attending ophthalmic surgeon:	
Comments: _____ _____	
Signature of person completing above fields **Signature: _____ Date: _____**	

15.3.2 Pre-Procedure and Randomization CRF (Sample)

PRE-PROCEDURE AND RANDOMIZATION CHECKLIST

- □ Review inclusion/exclusion criteria eligibility
- □ Randomize
- □ Confirm pre-operative clearance
- □ Confirm date of surgical procedure
- □ Coordinate with investigational pharmacy services for medication

ELIGIBILITY CRITERIA REVIEW

INCLUSION CRITERIA ***Must be "yes"***	**Yes**	**No**	**Notes**
1. Age 18 years or older	☐	☐	
2. Ability to speak and read in English or Spanish or Haitian Creole	☐	☐	
3. Subjects able to consent for themselves	☐	☐	

4. Outpatient surgical plan for any of the following procedures:
• Cataract Surgery
  o Cataracts
• Retina
  o Pars plana vitrectomy (PPV)
  o PPV with cataracts, epiretinal membrane peel, pars plana lensectomy and/or endolaser
  o Silicone oil removal
• Cornea
  o DSEK
  o Cataracts with DSEK
  o DMEK
  o Cataracts with DMEK
  o Conjunctival and/or corneal lesion excisions
  o Pterygium
• Glaucoma
  o Ahmed valve
  o Ahmed valve with cataracts
  o Trabeculectomy
  o Trabeculectomy with cataracts
  o Baerveldt
  o Baerveldt with cataracts
  o Endocyclophotocoagulation
  o Endocyclophotocoagulation with cataracts
  o Istent
  o Istent with cataracts
  o Kahook
  o Kahook with cataracts
  o Cypass
  o Cypass with cataracts
	☐	☐	Category: ☐ cataracts
			☐ retina
			☐ cornea
			☐ glaucoma
			
			Name of Procedure: _____
			_____
			_____

EXCLUSION CRITERIA *Must be "no"*	**Yes**	**No**	**N/A at this time**	**Notes**
1. Surgical plan which includes general anesthesia	☐	☐	☐	
2. Hypersensitivity or allergy to benzodiazepines	☐	☐	☐	
3. Women who are pregnant, have a positive pregnancy test on the day of surgery, refuse a pregnancy test, or are nursing	☐	☐	☐	
4. Previous delirium after anesthesia with a benzodiazepine	☐	☐	☐	
5. Subject is 70 years of age or older and failed the delirium pre-screening questionnaire	☐	☐	☐	
6. Currently experiencing the effects of drugs/alcohol	☐	☐	☐	
7. Current oral/IV regimen of any medication inhibiting cytochrome P450 3A which includes ketoconazole, itraconazole, nefazodone, ritonavir, indinavir, nelavir, saquinavir, and lopinavir	☐	☐	☐	
8. Subjects already enrolled in this study for the fellow eye	☐	☐	☐	
9. Subjects enrolled in a clinical trial with an investigational drug within the past 3 months	☐	☐	☐	
10. Failed anesthesia clearance to receive a benzodiazepine	☐	☐	☐	

This subject is:

☐ **Eligible for participation** ☐ **Ineligible for participation**

Signed by study team member who is (1) qualified to assess eligibility and (2) delegated this study task by the PI

Signature:	**Date:**
Printed Name:	

PATIENT VITALS

Measured?	☐ Measured previously → *Complete Table A.* ☐ Not measured → *Complete Table B.* ☐ Re-measured → *Complete Table C.*
Table A *Patient Vitals were Measured Previously*	
Date vitals were taken:	Date: _____
Height	_____ feet _____ inches
Weight	_____ lbs.
BMI	
Do vitals need to be re-measured? *Vitals must be re-measured if they were not measured when consented in clinic, at an in-person pre-operative appointment, or at another appointment within the past month*	☐ Yes, they will be re-measured at: ☐ Pre-operative appointment ☐ On the day of surgery ☐ Other: _____ ☐ No → Vitals can be used for medication dosing
Table B *Patient Vitals were Not Measured*	
When will vitals be measured?	☐ At a pre-operative appointment ☐ On the day of surgery ☐ Other: _____
Table C *Patient Vitals were Re-measured*	
Date vitals were taken:	Date: _____
Height	_____ feet _____ inches
Weight	_____ lbs.
BMI	
Comments: _____ _____	
Signature of person completing above fields **Signature:** _____ **Date:** _____	

RANDOMIZATION

Was the subject randomized according to their study ID?	☐ YES → *Fill out table below.* ☐ NO → *Add comment below.*

Randomization ID:

Date of Randomization	**Name of Medication**	**Route**	**Sedation Dosage**
	Triazolam or placebo Microcrystalline cellulose	Oral	☐ 1 pill – *BMI < 35* ☐ 2 pills – *BMI ≥ 35*
	Midazolam or placebo Sodium Chloride 0.9%	IV	☐ 1 unit dose – *BMI < 35* ☐ 2 unit doses – *BMI ≥ 35*

Comments:

_____

_____

Signature of person completing above fields

Signature: _____ **Date:** _____

PRE-OPERATIVE CLEARANCE

Completed?	☐ Complete → *Complete Table A.* ☐ Incomplete → *Complete Table B.*
Table A *Pre-Operative Clearance was Completed*	
Date of completed pre-operative clearance:	Date: _____
Date of pre-operative clearance expiration:	Date: _____
Type of surgical pre-operative clearance	☐ Over the phone ☐ In-person
Table B *Pre-Operative Clearance was Not Completed*	
Date of rescheduled pre-operative clearance:	Date: _____
Type of surgical pre-operative clearance	☐ Over the phone ☐ In-person
Comments: _____ _____	
Signature of person completing above fields **Signature:** _____ **Date:** _____	

SURGICAL PROCEDURE DETAILS

Date of surgical procedure:	Date: _____
Name of surgical procedure:	Category: ☐ cataract ☐ retina ☐ cornea ☐ glaucoma Name of Procedure: _____ _____
Name of attending ophthalmic surgeon:	
Comments: _____ _____	
Signature of person completing above fields **Signature:** _____ **Date:** _____	

COORDINATION WITH INVESTIGATIONAL PHARMACY SERVICES

Tasks to be Completed	Yes	No *If "no", write a comment*	Comments
1. Send calendar invite to IPS with surgical date	☐	☐	
2. Send pharmacy signed consent form page	☐	☐	
3. Send pharmacy EPIC order	☐	☐	
4. Send pharmacy documentation of randomization	☐	☐	
Comments: _____ _____			
Signature of person completing above fields **Signature:** _____ **Date:** _____			

15.3.3 Day of Surgical Procedure CRF (Sample)

DAY OF SURGICAL PROCEDURE CHECKLIST

- □ Re-consent under current informed consent form (if required)
- □ Administer pregnancy test (if female of childbearing potential)
- □ Review inclusion/exclusion criteria eligibility
- □ Confirm if pre-operative clearance
- □ Obtain medication from IPS
- □ Administer medication
- □ Complete Anesthesiologist/CRNA Survey
- □ Complete Attending Surgeon Survey
- □ Document additional anesthesia measures
- □ Documentation of anesthesia intraoperative complications
- □ Documentation of ocular intraoperative complications
- □ Document of completed surgical procedure
- □ Assess of possible AEs and/or SAEs
- □ Discharge with post-operative day 1 appointment

INFORMED CONSENT

<table>
<tr><td rowspan="3">Was the subject re-consented to current version?</td><td>☐ Yes

Version: _____

Date: _____
Time (24 hour clock): ___ ___ : ___ ___

Was subject given a copy of the signed consent form with contact information?
☐ Yes
☐ No → Add comment below.</td></tr>
<tr><td>☐ No</td></tr>
<tr><td>☐ N/A – Subject is already consented under current version.</td></tr>
<tr><td colspan="2">Comments:

_____

_____</td></tr>
<tr><td colspan="2">Signature of person completing above fields

Signature: _____ Date: _____</td></tr>
</table>

PREGNANCY TEST ADMINISTRATION

PREGNANCY TEST ADMINISTRATION	
Sex of Patient:	☐ Male → *Form is complete.* ☐ Female → *Continue to next question.*
Is the patient of childbearing potential?	☐ YES → *Continue to next question.* ☐ NO → *Form is complete.*

Time of administration: ___ ___ : ___ ___ (24 hour clock)

Pregnancy Test Results:

- ☐ Positive → *Patient is INELIGIBLE for study.*
- ☐ Negative → *Patient is ELIGIBLE for study.*

Comments:

_____

_____

Signature of person completing above fields

Signature: _____ **Date:** _____

ELIGIBILITY CRITERIA REVIEW

INCLUSION CRITERIA ***Must be "yes"***	**Yes**	**No**	**Notes**
1. Age 18 years or older	☐	☐	
2. Ability to speak and read in English or Spanish or Haitian Creole	☐	☐	
3. Subjects able to consent for themselves	☐	☐	

4. Outpatient surgical plan for any of the following procedures:
• Cataract Surgery
  o Cataracts
• Retina
  o Pars plana vitrectomy (PPV)
  o PPV with cataracts, epiretinal membrane peel, pars plana lensectomy and/or endolaser
  o Silicone oil removal
• Cornea
  o DSEK
  o Cataracts with DSEK
  o DMEK
  o Cataracts with DMEK
  o Conjunctival and/or corneal lesion excisions
  o Pterygium
• Glaucoma
  o Ahmed valve
  o Ahmed valve with cataracts
  o Trabeculectomy
  o Trabeculectomy with cataracts
  o Baerveldt
  o Baerveldt with cataracts
  o Endocyclophotocoagulation
  o Endocyclophotocoagulation with cataracts
  o Istent
  o Istent with cataracts
  o Kahook
  o Kahook with cataracts
  o Cypass
  o Cypass with cataracts
	☐	☐	Category: ☐ cataracts
			☐ retina
			☐ cornea
			☐ glaucoma
			
			Name of Procedure: _____
			_____
			_____

EXCLUSION CRITERIA *Must be "no"*	Yes	No	N/A at this time	Notes
1. Surgical plan which includes general anesthesia	☐	☐	☐	
2. Hypersensitivity or allergy to benzodiazepines	☐	☐	☐	
3. Women who are pregnant, have a positive pregnancy test on the day of surgery, refuse a pregnancy test, or are nursing	☐	☐	☐	
4. Previous delirium after anesthesia with a benzodiazepine	☐	☐	☐	
5. Subject is 70 years of age or older and failed the delirium pre-screening questionnaire	☐	☐	☐	
6. Currently experiencing the effects of drugs/alcohol	☐	☐	☐	
7. Current oral/IV regimen of any medication inhibiting cytochrome P450 3A which includes ketoconazole, itraconazole, nefazodone, ritonavir, indinavir, nelavir, saquinavir, and lopinavir	☐	☐	☐	
8. Subjects already enrolled in this study for the fellow eye	☐	☐	☐	
9. Subjects enrolled in a clinical trial with an investigational drug within the past 3 months	☐	☐	☐	
10. Failed anesthesia clearance to receive a benzodiazepine	☐	☐	☐	

This subject is:

☐ **Eligible for participation** ☐ **Ineligible for participation**

Signed by study team member who is (1) qualified to assess eligibility and (2) delegated this study task by the PI

Signature:	**Date:**
Printed Name:	

PRE-OPERATIVE CLEARANCE CONFIRMATION

Completed?	☐ Complete – *complete table A* ☐ Incomplete – *complete table B*
Table A *Pre-Operative Clearance was Completed*	
Date of completed pre-operative clearance:	
Date of pre-operative clearance expiration:	
Table B *Pre-Operative Clearance was Not Completed*	
Will the surgery be re-scheduled?	☐ Yes – *re-complete "Before Surgery" forms* ☐ No – *subject will be dropped from the study*
Comments: _____ _____	
Signature of person completing above fields **Signature:** _____ **Date:** _____	

PATIENT VITALS

Measured?	☐ Measured previously → *Complete Table A.* ☐ Re-measured → *Complete Table B* ☐ Not measured → *Write comment below*
Table A *Patient Vitals were Measured Previously*	
Date vitals were taken:	Date: _____
Height	_____ feet _____ inches
Weight	_____ lbs.
BMI	
Do vitals need to be re-measured? *Vitals must be re-measured if they were not measured when consented in clinic, at an in-person pre-operative appointment, or at another appointment within the past month*	☐ Yes → Complete table B ☐ No → Vitals can be used for medication dosing
Table B *Patient Vitals were Re-measured*	
Date vitals were taken:	Date: _____
Height	_____ feet _____ inches
Weight	_____ lbs.
BMI	
Comments: _____ _____	
Signature of person completing above fields **Signature:** _____ **Date:** _____	

MEDICATION DISPENSING

Tasks to be Completed	Yes	No *If "no", write a comment*	Comments
1. Send calendar invite to IPS with surgical date	☐	☐	
2. Send pharmacy signed consent form page	☐	☐	
3. Send pharmacy EPIC order	☐	☐	
4. Send pharmacy confirmation of randomization	☐	☐	
5. Confirm randomized medication dose	☐	☐	
Comments: _____ _____			
Signature of person completing above fields **Signature: _____ Date: _____**			

MEDICATION ADMINISTRATION

Were the randomized medications administered to the subject?	☐ YES → *Fill out table below.* ☐ NO → *Add comment below.*

Randomization ID:

If any non-study specific anesthetic interventions taken during pre-operative care, the procedure, and/or post-operative care, please document appropriately below.

Time Administered 24-hour clock	**Name of Medication**	**Route**	**Sedation Dosage**
___ ___ : ___ ___	Triazolam or placebo Microcrystalline cellulose	Oral	☐ 1 pill – *BMI < 35* ☐ 2 pills – *BMI ≥ 35*
___ ___ : ___ ___	Midazolam or placebo Sodium Chloride 0.9%	IV	☐ 1 unit dose – *BMI < 35* ☐ 2 unit doses – *BMI ≥ 35*

Comments:

_____

_____

Signature of person completing above fields

Signature: _____ **Date:** _____

SURGICAL PROCEDURE DETAILS

Date and time surgical procedure start:	Date: _____ Time (24 hour clock): ___ ___ : ___ ___
Date and time surgical procedure end:	Date: _____ Time (24 hour clock): ___ ___ : ___ ___
Name of completed surgical procedure:	Category: ☐ cataracts ☐ retina ☐ cornea ☐ glaucoma Name of Procedure: _____ _____
Type of Local Anesthesia Used	☐ Topical ☐ Subconjunctival ☐ Subtenon's ☐ Retrobulbar or peribulbar ☐ Other:
Name of attending ophthalmic surgeon:	
Comments: _____ _____	
Signature of person completing above fields **Signature:** _____ **Date:** _____	

ADDITIONAL ANESTHESIA INTERVENTIONS

Were additional anesthesia interventions utilized (e.g., administration of medications other than the study medication) during the procedure?	☐ YES → *Fill out table below.* ☐ NO → *Form is complete.*

If any non-study specific anesthetic interventions taken during pre-operative care, the procedure, and/or post-operative care, please document appropriately below.

Time Administered 24-hour clock	**Name of Medication**	**Route**	**Dosage**	**Reason for administration**
___ ___ : ___ ___		☐ Oral ☐ IV	☐ mg ☐ mL	
___ ___ : ___ ___		☐ Oral ☐ IV	☐ mg ☐ mL	
___ ___ : ___ ___		☐ Oral ☐ IV	☐ mg ☐ mL	
___ ___ : ___ ___		☐ Oral ☐ IV	☐ mg ☐ mL	
___ ___ : ___ ___		☐ Oral ☐ IV	☐ mg ☐ mL	
___ ___ : ___ ___		☐ Oral ☐ IV	☐ mg ☐ mL	
___ ___ : ___ ___		☐ Oral ☐ IV	☐ mg ☐ mL	

Comments:

____

____

Signature of person completing above fields

Signature: ______________________________ **Date:** ____________________

ANESTHESIA INTRAOPERATIVE COMPLICATIONS

Complication	Yes	No	Comments
Respiratory obstruction	☐	☐	
Hypercapnia	☐	☐	
Hypocapnia	☐	☐	
Hypoventilation	☐	☐	
Hypoxemia	☐	☐	
Hypertension	☐	☐	
Hypotension	☐	☐	
Cardiac arrhythmias	☐	☐	
Hypothermia	☐	☐	
Hyperthermia	☐	☐	
Itching	☐	☐	
Anaphylaxis	☐	☐	
Other: _____	☐	☐	
Comments: _____ _____			
Signature of person completing above fields **Signature:** _____ **Date:** _____			

OCULAR INTRAOPERATIVE COMPLICATIONS

Complication	Yes	No	Comments
Corneal burn	☐	☐	
Descemet Detachment	☐	☐	
Hyphema	☐	☐	
Iris prolapse	☐	☐	
Floppy iris syndrome	☐	☐	
Iridodialysis	☐	☐	
Dropped nucleus	☐	☐	
Retained lens fragment	☐	☐	
Anterior capsule tear	☐	☐	
Posterior capsule tear	☐	☐	
Aqueous misdirection	☐	☐	
Suprachoroidal hemorrhage	☐	☐	
Other: _____	☐	☐	

Comments:

_____

_____

Signature of person completing above fields

Signature: _____ **Date:** _____

ANESTHESIOLOGIST/CRNA SURVEY SCORING

Anesthesiologist/CRNA Responses Scoring Sheet Part 1		
Question	Response	Point Equivalent
1. The patient's pain level was well controlled	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
2. The patient's anxiety level was well controlled	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
3. Intravenous (IV) medication was required for breakthrough pain during surgery	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
4. There was no undesired movement	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
5. The patient was cooperative	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points

Anesthesiologist/CRNA Responses Scoring Sheet Part 2		
Question	Response	Point Equivalent
6. There was no operative deviation or complication as a result of the patients initial anesthesia medication a. Type of complication/deviation (if any): _____ _____	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points

Final Anesthesiologist/CRNA Satisfaction Survey Score Determination	
Question Number	Point(s)
1	
2	
3	
4	
5	
6	
Final Anesthesiologist Satisfaction Score *Average points for questions 1-6*	
Comments: _____ _____	
Signature of person completing above fields **Signature:** _____ **Date:** _____	

ATTENDING OPHTHALMOLOGIST SURGEON SURVEY SCORING

Surgeon Responses Scoring Sheet Part 1		
Question	Response	Point Equivalent
1. I was satisfied with the anesthesia administered during surgery	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
2. The patient's pain level was well controlled	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
3. The patient's anxiety level was well controlled	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
4. There was no undesired movement	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
5. The patient was cooperative	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points

Surgeon Responses Scoring Sheet Part 2		
Question	Response	Point Equivalent
6. There was no deviation from the operative standard that occurred as a result of the patient's initial anesthesia medication a. Type of complication/deviation (if any): _____ _____	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
7. Did you need to request additional pain medications from the anesthesiologist?	☐ Yes	Non-scoring
	☐ No	

Final Surgeon Satisfaction Survey Score Determination	
Question Number	Point(s)
1	
2	
3	
4	
5	
6	
Final Surgeon Satisfaction Score *Average points for questions 1-6*	
Comments: _____ _____	
Signature of person completing above fields **Signature:** _____ **Date:** _____	

ADVERSE EVENT(S) ASSESSMENT

Were any adverse events experienced?	☐ YES → *Fill out table below.* ☐ NO → *Form is complete.*

If any adverse events took place during pre-operative care, the procedure, and/or post-operative care, please document below, add to the adverse event log, and appropriate reports.

Time of Event 24-hour clock	**Name of Event**	**Notes**
___ ___ : ___ ___		
___ ___ : ___ ___		
___ ___ : ___ ___		
___ ___ : ___ ___		
___ ___ : ___ ___		
___ ___ : ___ ___		
___ ___ : ___ ___		

Comments:

_____

_____

Signature of person completing above fields

Signature: _____ **Date:** _____

DAY OF SURGICAL PROCEDURE DISCHARGE AND NEXT VISIT

Discharge Instructions – Scheduled Next Visit (+2 days from Surgical Procedure)		
□ Instruct subject to contact site immediately if extreme pain, nausea, vomiting, or shortness of breath is experienced. □ Discharge with emergency contact instructions. □ Discharge with instructions for post-operative day 1 visit.		
What is the date/time agreed with the subject for returning for the post-operative day 1 visit?	Date: _____	Time: ___ ___ : ___ ___

15.3.4 Post-Operative Day 1 CRF (Sample)

POST-OPERATIVE DAY 1 CHECKLIST

- □ Re-consent under current informed consent form (if required)
- □ Complete patient satisfaction survey
- □ Assessment of possible AEs and/or SAEs
- □ Dispense $25 ClinCard to reimburse for travel expenses
- □ Send home with follow-up instructions

INFORMED CONSENT

<table>
<tr><td rowspan="3">Was the subject re-consented to current version?</td><td>☐ Yes

Version: _____

Date: _____
Time (24 hour clock): ___ ___ : ___ ___

Was subject given a copy of the signed consent form with contact information?
☐ Yes
☐ No → Add comment below.</td></tr>
<tr><td>☐ No</td></tr>
<tr><td>☐ N/A – Subject is already consented under current version.</td></tr>
<tr><td colspan="2">Comments:

_____

_____</td></tr>
<tr><td colspan="2">Signature of person completing above fields

Signature: _____ Date: _____</td></tr>
</table>

PATIENT SATISFACTION SURVEY SCORING

Subject Responses Scoring Sheet Part 1		
Question	Response	Point Equivalent
1. I hurt during my surgery	☐ Disagree very much	☐ 6 point
	☐ Disagree	☐ 5 points
	☐ Disagree a little	☐ 4 points
	☐ Agree a little	☐ 3 points
	☐ Agree	☐ 2 points
	☐ Agree very much	☐ 1 points
2. I felt good during surgery	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
3. I felt pain during surgery	☐ Disagree very much	☐ 6 point
	☐ Disagree	☐ 5 points
	☐ Disagree a little	☐ 4 points
	☐ Agree a little	☐ 3 points
	☐ Agree	☐ 2 points
	☐ Agree very much	☐ 1 points
4. I was satisfied with the anesthesia care during surgery	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points

Subject Responses Scoring Sheet Part 2		
Question	Response	Point Equivalent
5. I itched during surgery	☐ Disagree very much	☐ 6 point
	☐ Disagree	☐ 5 points
	☐ Disagree a little	☐ 4 points
	☐ Agree a little	☐ 3 points
	☐ Agree	☐ 2 points
	☐ Agree very much	☐ 1 points
6. I felt relaxed during surgery	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
7. I felt safe during surgery	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
8. I threw up after surgery	☐ Disagree very much	☐ 6 point
	☐ Disagree	☐ 5 points
	☐ Disagree a little	☐ 4 points
	☐ Agree a little	☐ 3 points
	☐ Agree	☐ 2 points
	☐ Agree very much	☐ 1 points
9. I felt like throwing up after surgery	☐ Disagree very much	☐ 6 point
	☐ Disagree	☐ 5 points
	☐ Disagree a little	☐ 4 points
	☐ Agree a little	☐ 3 points
	☐ Agree	☐ 2 points
	☐ Agree very much	☐ 1 points

Subject Responses Scoring Sheet Part 3		
Question	Response	Point Equivalent
10. I would have the same anesthetic again	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
11. I was too hot or too cold during surgery	☐ Disagree very much	☐ 6 point
	☐ Disagree	☐ 5 points
	☐ Disagree a little	☐ 4 points
	☐ Agree a little	☐ 3 points
	☐ Agree	☐ 2 points
	☐ Agree very much	☐ 1 points
12. My pain level was as expected and well controlled during surgery	☐ Disagree very much	☐ 1 point
	☐ Disagree	☐ 2 points
	☐ Disagree a little	☐ 3 points
	☐ Agree a little	☐ 4 points
	☐ Agree	☐ 5 points
	☐ Agree very much	☐ 6 points
13. During your operation, your anesthesiologist gave you a medication to make you feel more calm, relaxed and/or sleepy. If you were to have this type of surgery again, would you prefer:	☐ More medicine	Non-scoring
	☐ Same medicine	
	☐ Less medicine	
	☐ No medicine	

Final Patient Satisfaction Survey Score Determination	
Question Number	Point(s)
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
Final Patient Satisfaction Score *Average points for questions 1-12*	

Comments:

_____

_____

Signature of person completing above fields

Signature: _____ **Date:** _____

ADVERSE EVENT(S) ASSESSMENT

Were any adverse events experienced?	☐ YES → *Fill out table below.* ☐ NO → *Form is complete.*

If any adverse events took place since discharge from the hospital, please document below, add to the adverse event log, and appropriate reports.

Date of Event	**Time of Event** *(If available)* 24-hour clock	**Brief Description of Event**	**Notes**
	___ ___ : ___ ___		
	___ ___ : ___ ___		
	___ ___ : ___ ___		
	___ ___ : ___ ___		
	___ ___ : ___ ___		
	___ ___ : ___ ___		
	___ ___ : ___ ___		

Comments:

_____

_____

Signature of person completing above fields

Signature: _____ **Date:** _____

STUDY COMPLETION AND DISCHARGE

Discharge Instructions – Scheduled Post-Operative Visits		
□ Instruct subject to contact site immediately if extreme pain, nausea, vomiting, or shortness of breath is experienced. □ Discharge with emergency contact instructions. □ Discharge with instructions for post-operative week 1 and month 1 visit. □ Dispense $25 ClinCard to reimburse of travel expenses		
What is the date/time agreed with the subject for returning for post-operative week 1 visit?	Date: _____	Time: ___ ___ : ___ ___

15.4 Midazolam Package Insert

MIDAZOLAM- midazolam injection
West-Ward Pharmaceuticals Corp.

Midazolam Injection, USP

CIV
Rx only

NOT FOR USE IN NEONATES
CONTAINS BENZYL ALCOHOL

BOXED WARNING

WARNINGS

Personnel and Equipment for Monitoring and Resuscitation
Adults and Pediatrics: **Intravenous midazolam has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous midazolam should be used only in hospital or ambulatory care settings, including physicians' and dental offices, that provide for continuous monitoring of respiratory and cardiac function, e.g., pulse oximetry. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and personnel trained in their use and skilled in airway management should be assured. (See WARNINGS.) For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.**

Risks From Concomitant Use With Opioids
Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Monitor patients for respiratory depression and sedation (see WARNINGS, PRECAUTIONS; Drug Interactions).

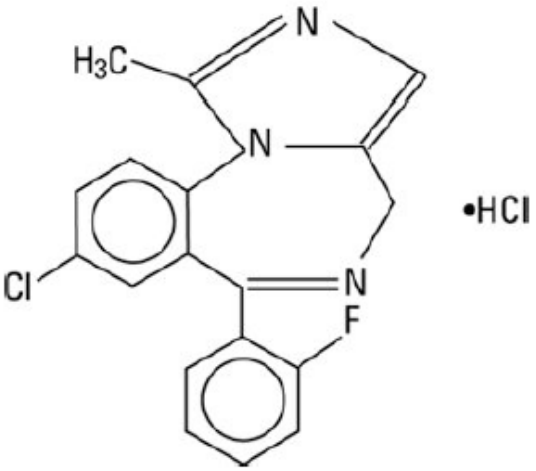
Individualization of Dosage
Midazolam should never be used without individualization of dosage. The initial intravenous dose for sedation in adult patients may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other central nervous system (CNS) depressants. The initial dose and all subsequent doses should always be titrated slowly; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Doses of sedative medications in pediatric patients must be calculated on a mg/kg basis, and initial doses and all subsequent doses should always be titrated slowly. The initial pediatric dose of midazolam for sedation/anxiolysis/amnesia is age, procedure and route dependent (see DOSAGE AND ADMINISTRATION for complete dosing information).

Neonates: **Midazolam should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid IV administration, particularly with concomitant use of fentanyl (see DOSAGE AND ADMINISTRATION for complete information).**

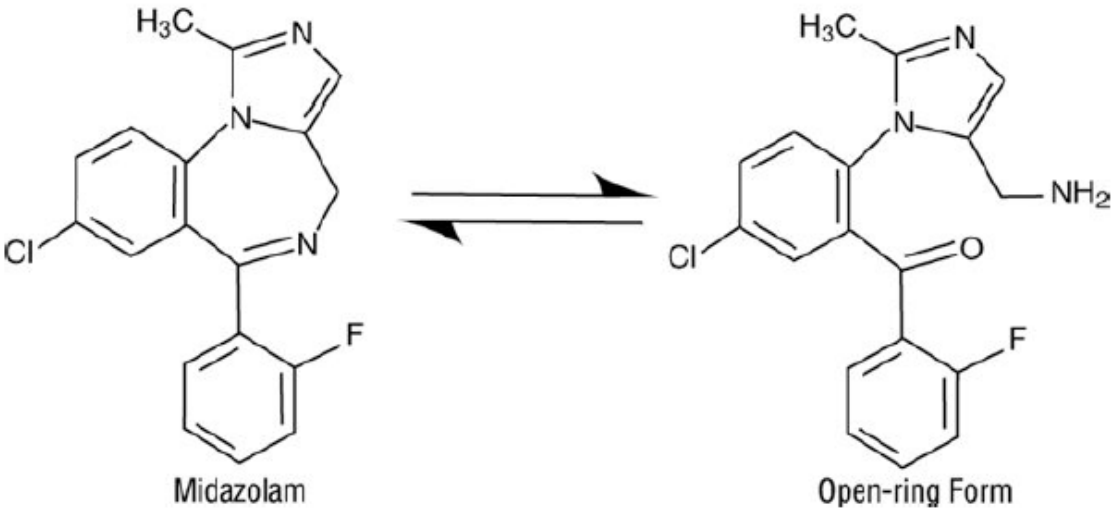
DESCRIPTION

Midazolam hydrochloride is a water-soluble benzodiazepine available as a sterile, nonpyrogenic parenteral dosage form for intravenous or intramuscular injection. Each mL contains midazolam hydrochloride equivalent to 1 mg or 5 mg midazolam in sterile water for injection. In addition, each mL contains the following inactive ingredients: 0.8% sodium chloride and 0.01% edetate disodium, with 1% benzyl alcohol as preservative; the pH is adjusted to 2.5-3.7 with sodium hydroxide and, if necessary, hydrochloric acid.

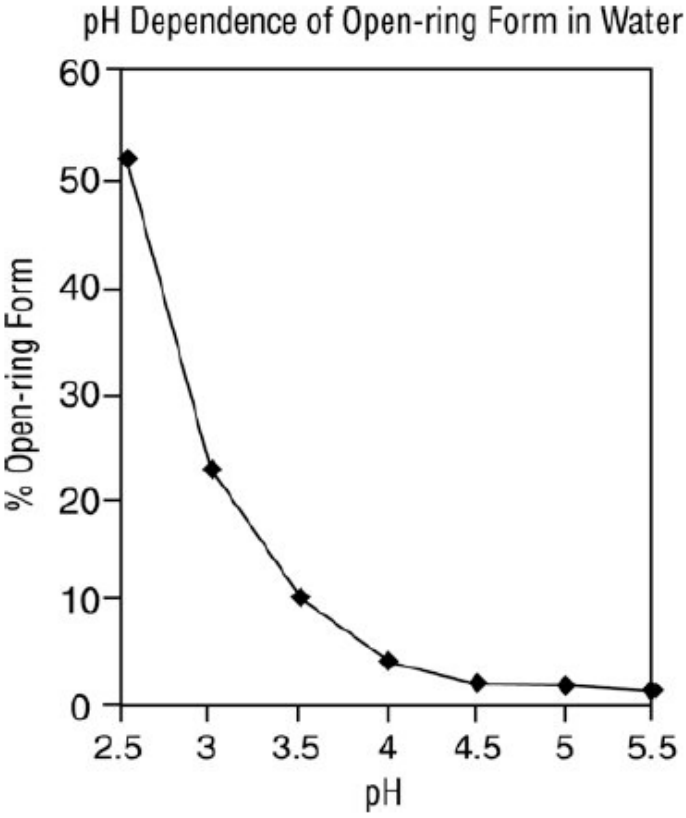
Midazolam is a white to light yellow crystalline compound, insoluble in water. The hydrochloride salt of midazolam, which is formed *in situ*, is soluble in aqueous solutions. Chemically, midazolam HCl is 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-a][1,4]benzodiazepine hydrochloride. Midazolam hydrochloride has the molecular formula $C_{18}H_{13}ClFN_3 \cdot HCl$, a calculated molecular weight of 362.25 and the following structural formula:



Under the acidic conditions required to solubilize midazolam in the product, midazolam is present as an equilibrium mixture (shown below) of the closed-ring form and an open-ring structure formed by the acid-catalyzed ring opening of the 4,5-double bond of the diazepine ring. The amount of open-ring form is dependent upon the pH of the solution. At the specified pH of the product, the solution may contain up to about 25% of the open-ring compound. At the physiologic conditions under which the product is absorbed (pH of 5 to 8) into the systemic circulation, any open-ring form present reverts to the physiologically active, lipophilic, closed-ring form (midazolam) and is absorbed as such.



The following chart plots the percentage of midazolam present as the open-ring form as a function of pH in aqueous solutions. As indicated in the graph, the amount of open-ring compound present in solution is sensitive to changes in pH over the pH range specified for the product: 2.5 to 3.7. Above pH 5, at least 99% of the mixture is present in the closed-ring form.



CLINICAL PHARMACOLOGY

Midazolam is a short-acting benzodiazepine central nervous system (CNS) depressant.

Pharmacodynamics:

The effects of midazolam on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other medications. Onset time of sedative effects after IM administration in adults is 15 minutes, with peak sedation occurring 30 to 60 minutes following injection. In one adult study, when tested the following day, 73% of the patients who received midazolam intramuscularly had no recall of memory cards shown 30 minutes following drug administration; 40% had no recall of the memory cards shown 60 minutes following drug administration. Onset time of sedative effects in the pediatric population begins within 5 minutes and peaks at 15 to 30 minutes depending upon the dose administered. In pediatric patients, up to 85% had no recall of pictures shown after receiving intramuscular midazolam compared with 5% of the placebo controls.

Sedation in adult and pediatric patients is achieved within 3 to 5 minutes after intravenous (IV) injection; the time of onset is affected by total dose administered and the concurrent administration of narcotic premedication. Seventy-one percent of the adult patients in endoscopy studies had no recall of introduction of the endoscope; 82% of the patients had no recall of withdrawal of the endoscope. In one study of pediatric patients undergoing lumbar puncture or bone marrow aspiration, 88% of patients had impaired recall vs 9% of the placebo controls. In another pediatric oncology study, 91% of midazolam treated patients were amnestic compared with 35% of patients who had received fentanyl alone.

When midazolam is given IV as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when narcotic premedication has been administered and in 2 to 2.5 minutes without narcotic premedication or other sedative premedication. Some impairment in a test of memory was noted in 90% of the patients studied. A dose response study of pediatric patients premedicated with 1.0 mg/kg intramuscular (IM) meperidine found that only 4 out of 6 pediatric patients who received 600 mcg/kg IV midazolam lost consciousness, with eye closing at 108 ± 140 seconds. This group was compared with pediatric patients who were given thiopental 5 mg/kg IV; 6 out of 6 closed their eyes at 20 ± 3.2 seconds. Midazolam did not dependably induce anesthesia at this dose despite concomitant opioid administration in pediatric patients.

Midazolam, used as directed, does not delay awakening from general anesthesia in adults. Gross tests of recovery after awakening (orientation, ability to stand and walk, suitability for discharge from the recovery room, return to baseline Trieger competency) usually indicate recovery within 2 hours but recovery may take up to 6 hours in some cases. When compared with patients who received thiopental, patients who received midazolam generally recovered at a slightly slower rate. Recovery from anesthesia or sedation for procedures in pediatric patients depends on the dose of midazolam administered, coadministration of other medications causing CNS depression and duration of the procedure.

In patients without intracranial lesions, induction of general anesthesia with IV midazolam is associated with a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that observed following IV thiopental. Preliminary data in neurosurgical patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements) show comparable elevations of intracranial pressure with midazolam and with thiopental during intubation. No similar studies have been reported in pediatric patients.

The usual recommended intramuscular premedicating doses of midazolam do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent in adults. Intravenous induction doses of midazolam depress the ventilatory response to carbon dioxide stimulation for 15 minutes or more beyond the duration of ventilatory depression following administration of thiopental in adults. Impairment of ventilatory response to carbon dioxide is more marked in adult patients with chronic obstructive pulmonary disease (COPD). Sedation with IV midazolam does not adversely affect the mechanics of respiration (resistance, static recoil, most lung volume measurements); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at

50% of awake total lung capacity (V_{max}) increase. In one study of pediatric patients under general anesthesia, intramuscular midazolam (100 or 200 mcg/kg) was shown to depress the response to carbon dioxide in a dose related manner.

In cardiac hemodynamic studies in adults, IV induction of general anesthesia with midazolam was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Slow heart rates (less than 65/minute), particularly in patients taking propranolol for angina, tended to rise slightly; faster heart rates (e.g., 85/minute) tended to slow slightly. In pediatric patients, a comparison of IV midazolam (500 mcg/kg) with propofol (2.5 mg/kg) revealed a mean 15% decrease in systolic blood pressure in patients who had received IV midazolam vs a mean 25% decrease in systolic blood pressure following propofol.

Pharmacokinetics:

Midazolam's activity is primarily due to the parent drug. Elimination of the parent drug takes place via hepatic metabolism of midazolam to hydroxylated metabolites that are conjugated and excreted in the urine. Six single-dose pharmacokinetic studies involving healthy adults yield pharmacokinetic parameters for midazolam in the following ranges: volume of distribution (Vd), 1.0 to 3.1 L/kg; elimination half-life, 1.8 to 6.4 hours (mean approximately 3 hours); total clearance (Cl), 0.25 to 0.54 L/hr/kg. In a parallel group study, there was no difference in the clearance, in subjects administered 0.15 mg/kg (n=4) and 0.30 mg/kg (n=4) IV doses indicating linear kinetics. The clearance was successively reduced by approximately 30% at doses of 0.45 mg/kg (n=4) and 0.6 mg/kg (n=5) indicating non-linear kinetics in this dose range.

Absorption

The absolute bioavailability of the intramuscular route was greater than 90% in a crossover study in which healthy subjects (n=17) were administered a 7.5 mg IV or IM dose. The mean peak concentration (C_{max}) and time to peak (T_{max}) following the IM dose was 90 ng/mL (20% cv) and 0.5 hr (50% cv). C_{max} for the 1-hydroxy metabolite following the IM dose was 8 ng/mL (T_{max}=1.0 hr).

Following IM administration, C_{max} for midazolam and its 1-hydroxy metabolite were approximately one-half of those achieved after intravenous injection.

Distribution

The volume of distribution (Vd) determined from six single-dose pharmacokinetic studies involving healthy adults ranged from 1.0-3.1 L/kg. Female gender, old age and obesity are associated with increased values of midazolam Vd. In humans, midazolam has been shown to cross the placenta and enter into fetal circulation and has been detected in human milk and CSF (see **Special Populations**).

In adults and children older than 1 year, midazolam is approximately 97% bound to plasma protein, principally albumin.

Metabolism

In vitro studies with human liver microsomes indicate that the biotransformation of midazolam is mediated by cytochrome P450-3A4. This cytochrome also appears to be present in gastrointestinal tract mucosa as well as liver. Sixty to seventy percent of the biotransformation products is 1-hydroxy-midazolam (also termed alpha-hydroxymidazolam) while 4-hydroxy-midazolam constitutes 5% or less. Small amounts of a dihydroxy derivative have also been detected but not quantified. The principal urinary excretion products are glucuronide conjugates of the hydroxylated derivatives.

Drugs that inhibit the activity of cytochrome P450-3A4 may inhibit midazolam clearance and elevate steady-state midazolam concentrations.

Studies of the intravenous administration of 1-hydroxy-midazolam in humans suggest that 1-hydroxy-midazolam is at least as potent as the parent compound and may contribute to the net pharmacologic

activity of midazolam. *In vitro* studies have demonstrated that the affinities of 1- and 4-hydroxy-midazolam for the benzodiazepine receptor are approximately 20% and 7%, respectively, relative to midazolam.

Excretion

Clearance of midazolam is reduced in association with old age, congestive heart failure, liver disease (cirrhosis) or conditions which diminish cardiac output and hepatic blood flow.

The principal urinary excretion product is 1-hydroxy-midazolam in the form of a glucuronide conjugate; smaller amounts of the glucuronide conjugates of 4-hydroxy- and dihydroxy-midazolam are detected as well. The amount of midazolam excreted unchanged in the urine after a single IV dose is less than 0.5% (n=5). Following a single IV infusion, in 5 healthy volunteers, 45% to 57% of the dose was excreted in the urine as 1-hydroxymethyl midazolam conjugate.

Pharmacokinetics-Continuous Infusion

The pharmacokinetic profile of midazolam following continuous infusion, based on 282 adult subjects, has been shown to be similar to that following single-dose administration for subjects of comparable age, gender, body habitus and health status. However, midazolam can accumulate in peripheral tissues with continuous infusion. The effects of accumulation are greater after long-term infusions than after short-term infusions. The effects of accumulation can be reduced by maintaining the lowest midazolam infusion rate that produces satisfactory sedation.

Infrequent hypotensive episodes have occurred during continuous infusion; however, neither the time to onset nor the duration of the episode appeared to be related to plasma concentrations of midazolam or alpha-hydroxy-midazolam. Further, there does not appear to be an increased chance of occurrence of a hypotensive episode with increased loading doses.

Patients with renal impairment may have longer elimination half-lives for midazolam (see **Special Populations:** Renal Failure).

Special Populations:

Changes in the pharmacokinetic profile of midazolam due to drug interactions, physiological variables, etc., may result in changes in the plasma concentration-time profile and pharmacological response to midazolam in these patients. For example, patients with acute renal failure appear to have a longer elimination half-life for midazolam and may experience delayed recovery (see **Special Populations: Renal Failure**). In other groups, the relationship between prolonged half-life and duration of effect has not been established.

Pediatrics and Neonates

In pediatric patients aged 1 year and older, the pharmacokinetic properties following a single dose of midazolam reported in 10 separate studies of midazolam are similar to those in adults. Weight-normalized clearance is similar or higher (0.19 to 0.80 L/hr/kg) than in adults and the terminal elimination half-life (0.78 to 3.3 hours) is similar to or shorter than in adults. The pharmacokinetic properties during and following continuous intravenous infusion in pediatric patients in the operating room as an adjunct to general anesthesia and in the intensive care environment are similar to those in adults.

In seriously ill neonates, however, the terminal elimination half-life of midazolam is substantially prolonged (6.5 to 12.0 hours) and the clearance reduced (0.07 to 0.12 L/hr/kg) compared to healthy adults or other groups of pediatric patients. It cannot be determined if these differences are due to age, immature organ function or metabolic pathways, underlying illness or debility.

Obese

In a study comparing normal (n=20) and obese patients (n=20) the mean half-life was greater in the obese

group (5.9 vs 2.3 hrs). This was due to an increase of approximately 50% in the Vd corrected for total body weight. The clearance was not significantly different between groups.

Geriatric

In three parallel group studies, the pharmacokinetics of midazolam administered IV or IM were compared in young (mean age 29, n=52) and healthy elderly subjects (mean age 73, n=53). Plasma half-life was approximately two-fold higher in the elderly. The mean Vd based on total body weight increased consistently between 15% to 100% in the elderly. The mean Cl decreased approximately 25% in the elderly in two studies and was similar to that of the younger patients in the other.

Congestive Heart Failure

In patients suffering from congestive heart failure, there appeared to be a two-fold increase in the elimination half-life, a 25% decrease in the plasma clearance and a 40% increase in the volume of distribution of midazolam.

Hepatic Impairment

Midazolam pharmacokinetics were studied after an IV single dose (0.075 mg/kg) was administered to 7 patients with biopsy-proven alcoholic cirrhosis and 8 control patients. The mean half-life of midazolam increased 2.5 fold in the alcoholic patients. Clearance was reduced by 50% and the Vd increased by 20%. In another study in 21 male patients with cirrhosis, without ascites and with normal kidney function as determined by creatinine clearance, no changes in the pharmacokinetics of midazolam or 1-hydroxy-midazolam were observed when compared to healthy individuals.

Renal Impairment

Patients with renal impairment may have longer elimination half-lives for midazolam and its metabolites which may result in slower recovery.

Midazolam and 1-hydroxy-midazolam pharmacokinetics in 6 ICU patients who developed acute renal failure (ARF) were compared with a normal renal function control group. Midazolam was administered as an infusion (5 to 15 mg/hr). Midazolam clearance was reduced (1.9 vs 2.8 mL/min/kg) and the half-life was prolonged (7.6 vs 13 hr) in the ARF patients. The renal clearance of the 1-hydroxy-midazolam glucuronide was prolonged in the ARF group (4 vs 136 mL/min) and the half-life was prolonged (12 hr vs >25 hr). Plasma levels accumulated in all ARF patients to about ten times that of the parent drug. The relationship between accumulating metabolite levels and prolonged sedation is unclear.

In a study of chronic renal failure patients (n=15) receiving a single IV dose, there was a 2-fold increase in the clearance and volume of distribution but the half-life remained unchanged. Metabolite levels were not studied.

Plasma Concentration-Effect Relationship

Concentration-effect relationships (after an IV dose) have been demonstrated for a variety of pharmacodynamic measures (e.g., reaction time, eye movement, sedation) and are associated with extensive intersubject variability. Logistic regression analysis of sedation scores and steady-state plasma concentration indicated that at plasma concentrations greater than 100 ng/mL there was at least a 50% probability that patients would be sedated, but respond to verbal commands (sedation score=3). At 200 ng/mL there was at least a 50% probability that patients would be asleep, but respond to glabellar tap (sedation score=4).

Drug Interactions

For information concerning pharmacokinetic drug interactions with midazolam, see **PRECAUTIONS**.

INDICATIONS AND USAGE

Midazolam Injection is indicated:

- intramuscularly or intravenously for preoperative sedation/anxiolysis/amnesia;
- intravenously as an agent for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suture of lacerations and other procedures either alone or in combination with other CNS depressants;
- intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous midazolam can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia);
- continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.

CONTRAINDICATIONS

Injectable midazolam is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow-angle glaucoma. Benzodiazepines may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam; patients with glaucoma have not been studied.

Midazolam Injection is not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol in the dosage form. Midazolam Injection is contraindicated for use in premature infants because the formulation contains benzyl alcohol. (See **WARNINGS** and **PRECAUTIONS: Pediatric Use**).

WARNINGS

Personnel and Equipment for Monitoring and Resuscitation

Prior to the intravenous administration of midazolam in any dose, the immediate availability of oxygen, resuscitative drugs, age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and skilled personnel for the maintenance of a patent airway and support of ventilation should be ensured. Patients should be continuously monitored for early signs of hypoventilation, airway obstruction, or apnea with means readily available (e.g., pulse oximetry). Hypoventilation, airway obstruction, and apnea can lead to hypoxia and/or cardiac arrest unless effective countermeasures are taken immediately. The immediate availability of specific reversal agents (flumazenil) is highly recommended. Vital signs should continue to be monitored during the recovery period. Because intravenous midazolam can depress respiration (see **CLINICAL PHARMACOLOGY**), especially when used concomitantly with opioid agonists and other sedatives (see **DOSAGE AND ADMINISTRATION**), it should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway, and supporting ventilation. When used for sedation/anxiolysis/amnesia, midazolam should always be titrated slowly in adult or pediatric patients. Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability; rapid intravenous administration should also be avoided in this population. See **DOSAGE AND ADMINISTRATION** for complete information.

Risks From Concomitant Use With Opioids

Concomitant use of benzodiazepines, including midazolam, and opioids may result in profound sedation, respiratory depression, coma, and death. If a decision is made to use midazolam concomitantly with opioids, monitor patients closely for respiratory depression and sedation (see **PRECAUTIONS; Drug Interactions**).

Risk of Respiratory Adverse Events

Serious cardiorespiratory adverse events have occurred after administration of midazolam. These have included respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death or permanent neurologic injury. There have also been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations particularly in adult or pediatric patients with hemodynamic instability. Hypotension occurred more frequently in the sedation studies in patients premedicated with a narcotic.

Individualization of Dosage

Midazolam must never be used without individualization of dosage particularly when used with other medications capable of producing central nervous system depression. See **DOSAGE AND ADMINISTRATION** for complete information.

Other Adverse Events

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported in both adult and pediatric patients. These reactions may be due to inadequate or excessive dosing or improper administration of midazolam; however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions. Should such reactions occur, the response to each dose of midazolam and all other drugs, including local anesthetics, should be evaluated before proceeding. Reversal of such responses with flumazenil has been reported in pediatric patients.

Concomitant Use of Central Nervous System Depressants

Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Debilitation and Comorbid Considerations

Higher risk adult and pediatric surgical patients, elderly patients and debilitated adult and pediatric patients require lower dosages, whether or not concomitant sedating medications have been administered. Adult or pediatric patients with COPD are unusually sensitive to the respiratory depressant effect of midazolam. Pediatric and adult patients undergoing procedures involving the upper airway such as upper endoscopy or dental care, are particularly vulnerable to episodes of desaturation and hypoventilation due to partial airway obstruction. Adult and pediatric patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly (see **CLINICAL PHARMACOLOGY**). Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduced initial dosage of midazolam is recommended, and the possibility of profound and/or prolonged effect should be considered.

Injectable midazolam should not be administered to adult or pediatric patients in shock or coma, or in acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of intravenous midazolam in adult or pediatric patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

Risk of Intra-arterial Injection

There have been limited reports of intra-arterial injection of midazolam. Adverse events have included local reactions, as well as isolated reports of seizure activity in which no clear causal relationship was established. Precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.

The safety and efficacy of midazolam following nonintravenous and nonintramuscular routes of administration have not been established. Midazolam should only be administered intramuscularly or intravenously.

Return to Full Cognitive Function

Midazolam is associated with a high incidence of partial or complete impairment of recall for the next several hours. The decision as to when patients who have received injectable midazolam, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized. Gross tests of recovery from the effects of midazolam (see **CLINICAL PHARMACOLOGY**) cannot be relied upon to predict reaction time under stress. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until one full day after anesthesia and surgery, whichever is longer. For pediatric patients, particular care should be taken to assure safe ambulation.

Usage in Pregnancy

An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) has been suggested in several studies. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see **DRUG ABUSE AND DEPENDENCE** section).

Usage in Preterm Infants and Neonates

Rapid injection should be avoided in the neonatal population. Midazolam administered rapidly as an intravenous injection (less than 2 minutes) has been associated with severe hypotension in neonates, particularly when the patient has also received fentanyl. Likewise, severe hypotension has been observed in neonates receiving a continuous infusion of midazolam who then receive a rapid intravenous injection of fentanyl. Seizures have been reported in several neonates following rapid intravenous administration.

The neonate also has reduced and/or immature organ function and is also vulnerable to profound and/or prolonged respiratory effects of midazolam.

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications (including midazolam) containing this preservative must take into account the total amount of benzyl alcohol administered. The recommended dosage range of midazolam for preterm and term infants includes amounts of benzyl alcohol well below that associated with toxicity; however, the amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (See **WARNINGS** and **PRECAUTIONS: Pediatric Use**).

Pediatric Neurotoxicity

Published animal studies demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive deficits when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the

first several months of life, but may extend out to approximately three years of age in humans (See **PRECAUTIONS: Pregnancy and Pediatric Use** and **ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY**).

Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anesthetic agents early in life and may result in adverse cognitive or behavioral effects. These studies have substantial limitations, and it is not clear if the observed effects are due to the anesthetic/sedation drug administration or other factors such as the surgery or underlying illness.

Anesthetic and sedation drugs are a necessary part of the care of children needing surgery, other procedures, or tests that cannot be delayed, and no specific medications have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

PRECAUTIONS

General

Intravenous doses of midazolam should be decreased for elderly and for debilitated patients (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**). These patients will also probably take longer to recover completely after midazolam administration for the induction of anesthesia.

Midazolam does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

The efficacy and safety of midazolam in clinical use are functions of the dose administered, the clinical status of the individual patient and the use of concomitant medications capable of depressing the CNS. Anticipated effects range from mild sedation to deep levels of sedation virtually equivalent to a state of general anesthesia where the patient may require external support of vital functions. Care must be taken to individualize and carefully titrate the dose of midazolam to the patient's underlying medical/surgical conditions, administer to the desired effect being certain to wait an adequate time for peak CNS effects of both midazolam and concomitant medications, and have the personnel and size-appropriate equipment and facilities available for monitoring and intervention (see **Boxed WARNING, WARNINGS** and **DOSAGE AND ADMINISTRATION**). Practitioners administering midazolam must have the skills necessary to manage reasonably foreseeable adverse effects, particularly skills in airway management. For information regarding withdrawal, see **DRUG ABUSE AND DEPENDENCE** section.

Information for Patients

To assure safe and effective use of benzodiazepines, the following information and instructions should be communicated to the patient when appropriate:

1. Inform your physician about any alcohol consumption and medicine you are now taking, especially blood pressure medication and antibiotics, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment.
2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.
4. Patients should be informed of the pharmacological effects of midazolam, such as sedation and amnesia, which in some patients may be profound. The decision as to when patients who have received injectable midazolam, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized.
5. Patients receiving continuous infusion of midazolam in critical care settings over an extended period of time may experience symptoms of withdrawal following abrupt discontinuation.
6. Effect of anesthetic and sedation drugs on early brain development

Studies conducted in young animals and children suggest repeated or prolonged use of general anesthetic or sedation drugs in children younger than 3 years may have negative effects on their developing brains. Discuss with parents and caregivers the benefits, risks, and timing and duration of surgery or procedures requiring anesthetic and sedation drugs.

Drug Interactions

Effect of Concomitant Use of Benzodiazepines and Opioids

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Monitor patients closely for respiratory depression and sedation.

Other CNS Depressants

The sedative effect of intravenous midazolam is accentuated by any concomitantly administered medication which depresses the central nervous system, particularly opioids (e.g., morphine, meperidine and fentanyl) and also secobarbital and droperidol. Consequently, the dosage of midazolam should be adjusted according to the type and amount of concomitant medications administered and the desired clinical response (see **DOSAGE AND ADMINISTRATION**).

Other Drug Interactions

Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the P450-3A4 enzyme system such as cimetidine (not ranitidine), erythromycin, diltiazem, verapamil, ketoconazole and itraconazole. These drug interactions may result in prolonged sedation due to a decrease in plasma clearance of midazolam.

The effect of single oral doses of 800 mg cimetidine and 300 mg ranitidine on steady-state concentrations of midazolam was examined in a randomized crossover study (n=8). Cimetidine increased the mean midazolam steady-state concentration from 57 to 71 ng/mL. Ranitidine increased the mean steady-state concentration to 62 ng/mL. No change in choice reaction time or sedation index was detected after dosing with the H_2 receptor antagonists.

In a placebo-controlled study, erythromycin administered as a 500 mg dose, tid, for 1 week (n=6), reduced the clearance of midazolam following a single 0.5 mg/kg IV dose. The half-life was approximately doubled.

Caution is advised when midazolam is administered to patients receiving erythromycin since this may result in a decrease in the plasma clearance of midazolam.

The effects of diltiazem (60 mg tid) and verapamil (80 mg tid) on the pharmacokinetics and pharmacodynamics of midazolam were investigated in a 3-way crossover study (n=9). The half-life of midazolam increased from 5 to 7 hours when midazolam was taken in conjunction with verapamil or diltiazem. No interaction was observed in healthy subjects between midazolam and nifedipine.

In a placebo-controlled study where saquinavir or placebo was administered orally as a 1200 mg dose, three times a day, for 5 days (n=12), a 56% reduction in the clearance of midazolam following a single 0.05 mg/kg IV dose was observed. The half-life was approximately doubled.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular midazolam for premedication in adults.

The intravenous administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of midazolam administered; no similar studies have been carried out in pediatric patients but there is no scientific reason to expect that pediatric patients would respond differently than adults.

Although the possibility of minor interactive effects has not been fully studied, midazolam and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration in adults. Midazolam does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the increased intracranial pressure noted following administration of succinylcholine. Midazolam does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine; no similar studies have been carried out in pediatric patients but there is no scientific reason to expect that pediatric patients would respond differently than adults.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine, and other nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed in adults or pediatric patients. In neonates, however, severe hypotension has been reported with concomitant administration of fentanyl. This effect has been observed in neonates on an infusion of midazolam who received a rapid injection of fentanyl and in patients on an infusion of fentanyl who have received a rapid injection of midazolam.

Drug/Laboratory Test Interactions

Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Midazolam maleate was administered with diet in mice and rats for 2 years at dosages of 1, 9 and 80 mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumors. In high-dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumors. Dosages of 9 mg/kg/day of midazolam maleate (25 times a human dose of 0.35 mg/kg) do not increase the incidence of tumors. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.

Mutagenesis

Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes or in the micronucleus test in mice.

Impairment of Fertility

Male rats were treated orally with 1, 4, or 16 mg/kg midazolam beginning 62 days prior to mating with female rats treated with the same doses for 14 days prior to mating to Gestation Day 13 or Lactation Day 21. The high dose produced an equivalent exposure (AUC) as 4 mg/kg intravenous midazolam (1.85 times the human induction dose of 0.35 mg/kg based on body surface area comparison). There were no adverse effects on either male or female fertility noted.

Pregnancy

Teratogenic Effects: Pregnancy Category D (see **WARNINGS**)

Published studies in pregnant primates demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see Data).

Data

Animal Data

Pregnant rats were treated with midazolam using intravenous doses of 0.2, 1, and 4 mg/kg/day (0.09, 0.46, and 1.85 times the human induction dose of 0.35 mg/kg based on body surface area comparisons) during the period of organogenesis (Gestation Day 7 through 15). Midazolam did not cause adverse effects to the fetus at doses of up to 1.85 times the human induction dose. All doses produced slight to moderate ataxia. The high dose produced a 5% decrease in maternal body weight gain compared to control.

Pregnant rabbits were treated with midazolam using intravenous doses of 0.2, 0.6, and 2 mg/kg/day (0.09, 0.46, and 1.85 times the human induction dose of 0.35 mg/kg based on body surface area comparisons) during the period of organogenesis (Gestation Day 7 to 18). Midazolam did not cause adverse effects to the fetus at doses of up to 1.85 times the human induction dose. The high dose was associated with findings of ataxia and sedation but no evidence of maternal toxicity.

Pregnant rats were administered midazolam using intravenous doses of 0.2, 1, and 4 mg/kg/day (0.09, 0.46, and 1.85 times the human induction dose of 0.35 mg/kg based on body surface area comparisons) during late gestation and through lactation (Gestation Day 15 through Lactation Day 21). All doses produced ataxia. The high dose produced a slight decrease in maternal body weight gain compared to control. There were no clear adverse effects noted in the offspring. The study included no functional assessments of the pups, such as learning and memory testing or reproductive capacity.

In a published study in primates, administration of an anesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the fetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits (See **WARNINGS: Pediatric Neurotoxicity**, **PRECAUTIONS: Pediatric Use**, and **ANIMAL PHARMACOLOGY AND/OR TOXICOLOGY**).

Labor and Delivery

In humans, measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, indicating placental transfer of the drug. Following intramuscular administration of 0.05 mg/kg of midazolam, both the venous and the umbilical arterial serum concentrations were lower than maternal concentrations.

The use of injectable midazolam in obstetrics has not been evaluated in clinical studies. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, midazolam is not recommended for obstetrical use.

Nursing Mothers

Midazolam is excreted in human milk. Caution should be exercised when midazolam is administered to a nursing woman.

Pediatric Use

The safety and efficacy of midazolam for sedation/anxiolysis/amnesia following single dose intramuscular administration, intravenously by intermittent injections and continuous infusion have been established in pediatric and neonatal patients. For specific safety monitoring and dosage guidelines see **Boxed WARNING**, **CLINICAL PHARMACOLOGY**, **INDICATIONS AND USAGE**, **WARNINGS**, **PRECAUTIONS**, **ADVERSE REACTIONS**, **OVERDOSAGE** and **DOSAGE AND ADMINISTRATION** sections. UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF MIDAZOLAM ON A MG/KG BASIS. As a group,

pediatric patients generally require higher dosages of midazolam (mg/kg) than do adults. Younger (less than six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require closer monitoring. In obese PEDIATRIC PATIENTS, the dose should be calculated based on ideal body weight. When midazolam is given in conjunction with opioids or other sedatives, the potential for respiratory depression, airway obstruction, or hypoventilation is increased. The health care practitioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation.

Midazolam should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid IV administration, particularly with concomitant use of fentanyl.

Midazolam injection contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome”, (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages greater than 99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Data

Animal Data

Published juvenile animal studies demonstrate that the administration of anesthetic and sedation drugs, such as Midazolam Injection USP, that either block NMDA receptors or potentiate the activity of GABA during the period of rapid brain growth or synaptogenesis, results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of ketamine that produced a light surgical plane of anesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer of isoflurane increased neuronal cell loss. Data from isoflurane-treated rodents and ketamine-treated primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory. The clinical significance of these nonclinical findings is not known, and healthcare providers should balance the benefits of appropriate anesthesia in pregnant women, neonates, and young children who require procedures with the potential risks suggested by the nonclinical data (See **WARNINGS: Pediatric Neurotoxicity**, **PRECAUTIONS: Pregnancy**, and **ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY**).

Geriatric Use

Because geriatric patients may have altered drug distribution and diminished hepatic and/or renal function, reduced doses of midazolam are recommended. Intravenous and intramuscular doses of midazolam should be decreased for elderly and for debilitated patients (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**) and subjects over 70 years of age may be particularly sensitive. These patients will also probably take longer to recover completely after midazolam administration for the induction of anesthesia. Administration of IM and IV midazolam to elderly and/or

high-risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially narcotics (see **DOSAGE AND ADMINISTRATION**).

Specific dosing and monitoring guidelines for geriatric patients are provided in the **DOSAGE AND ADMINISTRATION** section for premedicated patients for sedation/anxiolysis/amnesia following IV and IM administration, for induction of anesthesia following IV administration and for continuous infusion.

ADVERSE REACTIONS

See **WARNINGS** concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs were the most frequently seen findings following parenteral administration of midazolam in adults and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. The majority of serious adverse effects, particularly those associated with oxygenation and ventilation, have been reported when midazolam is administered with other medications capable of depressing the central nervous system. The incidence of such events is higher in patients undergoing procedures involving the airway without the protective effect of an endotracheal tube (e.g., upper endoscopy and dental procedures).

Adults

The following additional adverse reactions were reported after intramuscular administration:

headache (1.3%)	*Local effects at IM Injection site*
	pain (3.7%)
	induration (0.5%)
	redness (0.5%)
	muscle stiffness (0.3%)

Administration of IM midazolam to elderly and/or higher risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially narcotics (see **DOSAGE AND ADMINISTRATION**).

The following additional adverse reactions were reported subsequent to intravenous administration as a single sedative/anxiolytic/amnestic agent in adult patients:

hiccoughs (3.9%)	*Local effects at the IV site*
nausea (2.8%)	tenderness (5.6%)
vomiting (2.6%)	pain during injection (5.0%)
coughing (1.3%)	redness (2.6%)
“oversedation” (1.6%)	induration (1.7%)
headache (1.5%)	phlebitis (0.4%)
drowsiness (1.2%)	

Pediatric Patients

The following adverse events related to the use of IV midazolam in pediatric patients were reported in the medical literature: desaturation 4.6%, apnea 2.8%, hypotension 2.7%, paradoxical reactions 2.0%,

hiccough 1.2%, seizure-like activity 1.1% and nystagmus 1.1%. The majority of airway-related events occurred in patients receiving other CNS depressing medications and in patients where midazolam was not used as a single sedating agent.

Neonates

For information concerning hypotensive episodes and seizures following the administration of midazolam to neonates, see **Boxed WARNING, CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS** sections.

Other adverse experiences, observed mainly following IV injection as a single sedative/anxiolytic/amnesia agent and occurring at an incidence of <1.0% in adult and pediatric patients, are as follows:

Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea

Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm

Gastrointestinal: Acid taste, excessive salivation, retching

CNS/Neuromuscular: Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoidmovements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia

Special Sense: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, light-headedness

Integumentary: Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site

Hypersensitivity: Allergic reactions including anaphylactoid reactions, hives, rash, pruritus

Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma

DRUG ABUSE AND DEPENDENCE

Midazolam injection contains midazolam, a Schedule IV controlled substance.

Midazolam was actively self-administered in primate models used to assess the positive reinforcing effects of psychoactive drugs.

Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

Withdrawal symptoms similar in character to those noted with barbiturates and alcohol (convulsions, hallucinations, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuation of benzodiazepines, including midazolam. Abdominal distention, nausea, vomiting and tachycardia are prominent symptoms of withdrawal in infants. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. There is no consensus in the medical literature regarding tapering schedules; therefore, practitioners are advised to individualize therapy to meet patient's needs. In some case reports, patients who have had severe withdrawal reactions due to

abrupt discontinuation of high-dose long-term midazolam, have been successfully weaned off of midazolam over a period of several days.

OVERDOSAGE

Symptoms

The manifestations of midazolam overdosage reported are similar to those observed with other benzodiazepines, including sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma and untoward effects on vital signs. No evidence of specific organ toxicity from midazolam overdosage has been reported.

Treatment

Treatment of injectable midazolam overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation, including administration of oxygen. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of any value in the treatment of midazolam overdosage.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. There are anecdotal reports of reversal of adverse hemodynamic responses associated with midazolam following administration of flumazenil to pediatric patients. Prior to the administration of flumazenil, necessary measures should be instituted to secure the airway, assure adequate ventilation, and establish adequate intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. **Flumazenil will only reverse benzodiazepine-induced effects but will not reverse the effects of other concomitant medications.** The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk patients. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert, including **CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS**, should be consulted prior to use.

DOSAGE AND ADMINISTRATION

NOTE: CONTAINS BENZYL ALCOHOL (see **WARNINGS** and **PRECAUTIONS: Pediatric Use**)

The 1 mL and 2 mL Midazolam Injection vials include a cautionary label that extends above the main label and highlights the drug name and strength per total volume. The purpose of the extended label is to prevent medication errors due to the different strengths of Midazolam Injection. Read the label and confirm you have selected the correct medication and strength. Then locate the “Tear Here” point on the label, and remove this cautionary label prior to removing the flip-off cap.

Midazolam is a potent sedative agent that requires slow administration and individualization of dosage. Clinical experience has shown midazolam to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM MIDAZOLAM INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excessive

single doses or rapid intravenous administration may result in respiratory depression, airway obstruction and/or arrest. The potential for these latter effects is increased in debilitated patients, those receiving concomitant medications capable of depressing the CNS, and patients without an endotracheal tube but undergoing a procedure involving the upper airway such as endoscopy or dental (see **Boxed WARNING** and **WARNINGS**.)

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported in adult and pediatric patients. Should such reactions occur, caution should be exercised before continuing administration of midazolam (see **WARNINGS**).

Midazolam Injection should only be administered IM or IV (see **WARNINGS**).

Care should be taken to avoid intra-arterial injection or extravasation (see **WARNINGS**). Midazolam Injection may be mixed in the same syringe with the following frequently used premedications: morphine sulfate, meperidine, atropine sulfate or scopolamine. Midazolam, at a concentration of 0.5 mg/mL, is compatible with 5% dextrose in water and 0.9% sodium chloride for up to 24 hours and with lactated Ringer's solution for up to 4 hours. Both the 1 mg/mL and 5 mg/mL formulations of midazolam may be diluted with 0.9% sodium chloride or 5% dextrose in water.

Monitoring

Patient response to sedative agents, and resultant respiratory status, is variable. Regardless of the intended level of sedation or route of administration, sedation is a continuum; a patient may move easily from light to deep sedation, with potential loss of protective reflexes. This is especially true in pediatric patients. Sedative doses should be individually titrated, taking into account patient age, clinical status and concomitant use of other CNS depressants. Continuous monitoring of respiratory and cardiac function is required (i.e., pulse oximetry).

Adults and Pediatrics

Sedation guidelines recommend a careful presedation history to determine how a patient's underlying medical conditions or concomitant medications might affect their response to sedation/analgesia as well as a physical examination including a focused examination of the airway for abnormalities. Further recommendations include appropriate presedation fasting.

Titration to effect with multiple small doses is essential for safe administration. It should be noted that adequate time to achieve peak central nervous system effect (3 to 5 minutes) for midazolam should be allowed between doses to minimize the potential for oversedation. Sufficient time must elapse between doses of concomitant sedative medications to allow the effect of each dose to be assessed before subsequent drug administration. This is an important consideration for all patients who receive intravenous midazolam.

Immediate availability of resuscitative drugs and *age*- and *size-appropriate* equipment and personnel trained in their use and skilled in airway management should be assured (see **WARNINGS**).

Pediatrics

For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

Intravenous access is not thought to be necessary for all pediatric patients sedated for a diagnostic or therapeutic procedure because in some cases the difficulty of gaining IV access would defeat the purpose of sedating the child; rather, emphasis should be placed upon having the intravenous equipment available and a practitioner skilled in establishing vascular access in pediatric patients immediately available.

USUAL ADULT DOSE

INTRAMUSCULARLY

For preoperative sedation/anxiolysis/amnesia (induction of sleepiness or drowsiness and relief of apprehension and to impair memory of perioperative events).	The recommended premedication dose of midazolam for good risk (ASA Physical Status I & II) adult patients below the age of 60 years is 0.07 to 0.08 mg/kg IM (approximately 5 mg IM) administered up to 1 hour before surgery.
For intramuscular use, midazolam should be injected deep in a large muscle mass.	The dose must be individualized and reduced when IM midazolam is administered to patients with chronic obstructive pulmonary disease, other higher risk surgical patients, patients 60 or more years of age, and patients who have received concomitant narcotics or other CNS depressants (see **ADVERSE REACTIONS**). In a study of patients 60 years or older, who did not receive concomitant administration of narcotics, 2 to 3 mg (0.02 to 0.05 mg/kg) of midazolam produced adequate sedation during the preoperative period. The dose of 1 mg IM midazolam may suffice for some older patients if the anticipated intensity and duration of sedation is less critical. As with any potential respiratory depressant, these patients require observation for signs of cardiorespiratory depression after receiving IM midazolam. Onset is within 15 minutes, peaking at 30 to 60 minutes. It can be administered concomitantly with atropine sulfate or scopolamine hydrochloride and reduced doses of narcotics.

INTRAVENOUSLY

Sedation/anxiolysis/amnesia for procedures (See **INDICATIONS AND USAGE**): Narcotic premedication results in less variability in patient response and a reduction in dosage of midazolam. For peroral procedures, the use of an appropriate topical anesthetic is recommended. For bronchoscopic procedures, the use of narcotic premedication is recommended.	When used for sedation/anxiolysis/amnesia for a procedure, dosage must be individualized and titrated. Midazolam should always be titrated slowly; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. Individual response will vary with age, physical status and concomitant medications, but may also vary independent of these factors. (See **WARNINGS** concerning cardiac/respiratory arrest/airway obstruction/hypoventilation.)
Midazolam 1 mg/mL formulation is recommended for sedation/anxiolysis/amnesia for procedures to facilitate slower injection. Both the 1 mg/mL and the 5 mg/mL formulations may be diluted with 0.9% sodium chloride or 5% dextrose in water.	1. *Healthy Adults Below the Age of 60:* Titrate slowly to the desired effect, e.g., the initiation of slurred speech. Some patients may respond to as little as 1 mg. No more than 2.5 mg should be given over a period of at least 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If further titration is necessary, continue to titrate, using small increments, to the appropriate level of sedation. Wait an additional 2 or more minutes after each increment to fully evaluate the sedative effect. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint. If narcotic premedication or other CNS depressants are used, patients will require approximately 30% less midazolam than unpremedicated patients. 2. *Patients Age 60 or Older, and Debilitated or Chronically Ill Patients:* Because the danger of hypoventilation, airway

	obstruction, or apnea is greater in elderly patients and those with chronic disease states or decreased pulmonary reserve, and because the peak effect may take longer in these patients, increments should be smaller and the rate of injection slower. Titrate slowly to the desired effect, e.g., the initiation of slurred speech. Some patients may respond to as little as 1 mg. No more than 1.5 mg should be given over a period of no less than 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If additional titration is necessary, it should be given at a rate of no more than 1 mg over a period of 2 minutes, waiting an additional 2 or more minutes each time to fully evaluate the sedative effect. Total doses greater than 3.5 mg are not usually necessary. If concomitant CNS depressant premedications are used in these patients, they will require at least 50% less midazolam than healthy young unpremedicated patients. 3. *Maintenance Dose:* Additional doses to maintain the desired level of sedation may be given in increments of 25% of the dose used to first reach the sedative endpoint, but again only by slow titration, especially in the elderly and chronically ill or debilitated patient. These additional doses should be given only after a thorough clinical evaluation clearly indicates the need for additional sedation.
Induction of Anesthesia: For induction of general anesthesia, before administration of other anesthetic agents.	Individual response to the drug is variable, particularly when a narcotic premedication is not used. The dosage should be titrated to the desired effect according to the patient's age and clinical status. When midazolam is used before other intravenous agents for induction of anesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents. *Unpremedicated Patients:* In the absence of premedication, an average adult under the age of 55 years will usually require an initial dose of 0.3 to 0.35 mg/kg for induction, administered over 20 to 30 seconds and allowing 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used; induction may instead be completed with inhalational anesthetics. In resistant cases, up to 0.6 mg/kg total dose may be used for induction, but such larger doses may prolong recovery. Unpremedicated patients over the age of 55 years usually require less midazolam for induction; an initial dose of 0.3 mg/kg is recommended. Unpremedicated patients with severe systemic disease or other debilitation usually require less midazolam for induction. An initial dose of 0.2 to 0.25 mg/kg will usually suffice; in some cases, as little as 0.15 mg/kg may suffice. *Premedicated Patients:* When the patient has received sedative or narcotic premedication, particularly narcotic premedication, the range of

	recommended doses is 0.15 to 0.35 mg/kg. In average adults below the age of 55 years, a dose of 0.25 mg/kg, administered over 20 to 30 seconds and allowing 2 minutes for effect, will usually suffice. The initial dose of 0.2 mg/kg is recommended for good risk (ASA I & II) surgical patients over the age of 55 years. In some patients with severe systemic disease or debilitation, as little as 0.15 mg/kg may suffice. Narcotic premedication frequently used during clinical trials included fentanyl (1.5 to 2 mcg/kg IV, administered 5 minutes before induction), morphine (dosage individualized, up to 0.15 mg/kg IM), and meperidine (dosage individualized, up to 1 mg/kg IM). Sedative premedications were hydroxyzine pamoate (100 mg orally) and sodium secobarbital (200 mg orally). Except for intravenous fentanyl, administered 5 minutes before induction, all other premedications should be administered approximately 1 hour prior to the time anticipated for midazolam induction.
Injectable midazolam can also be used during maintenance of anesthesia, for surgical procedures, as a component of balanced anesthesia. Effective narcotic premedication is especially recommended in such cases.	Incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.

CONTINUOUS INFUSION

For continuous infusion, midazolam 5 mg/mL formulation is recommended diluted to a concentration of 0.5 mg/mL with 0.9% sodium chloride or 5% dextrose in water.	*Usual Adult Dose:* If a loading dose is necessary to rapidly initiate sedation, 0.01 to 0.05 mg/kg (approximately 0.5 to 4 mg for a typical adult) may be given slowly or infused over several minutes. This dose may be repeated at 10 to 15 minute intervals until adequate sedation is achieved. For maintenance of sedation, the usual initial infusion rate is 0.02 to 0.10 mg/kg/hr (1 to 7 mg/hr). Higher loading or maintenance infusion rates may occasionally be required in some patients. The lowest recommended doses should be used in patients with residual effects from anesthetic drugs, or in those concurrently receiving other sedatives or opioids. Individual response to midazolam is variable. The infusion rate should be titrated to the desired level of sedation, taking into account the patient's age, clinical status and current medications. In general, midazolam should be infused at the lowest rate that produces the desired level of sedation. Assessment of sedation should be performed at regular intervals and the midazolam infusion rate adjusted up or down by 25% to 50% of the initial infusion rate so as to assure adequate titration of sedation level. Larger adjustments or even a small incremental dose may be necessary if rapid changes in the level of sedation are indicated. In addition, the infusion rate should be decreased by 10% to 25% every few hours to find the minimum effective infusion rate. Finding the minimum effective infusion rate decreases the potential accumulation of midazolam and provides for the most rapid recovery once the infusion is terminated. Patients who exhibit agitation, hypertension or tachycardia in response to noxious stimulation, but who are otherwise adequately sedated, may benefit from concurrent administration of an opioid analgesic. Addition of an opioid will generally reduce the minimum effective midazolam infusion rate.

PEDIATRIC UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE

PATIENTS **INCREMENTS OF MIDAZOLAM ON A MG/KG BASIS.** As a group, pediatric patients generally require higher dosages of midazolam (mg/kg) than do adults. Younger (less than six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients and may require close monitoring (see tables below). In obese PEDIATRIC PATIENTS, the dose should be calculated based on ideal body weight. When midazolam is given in conjunction with opioids or other sedatives, the potential for respiratory depression, airway obstruction or hypoventilation is increased. For appropriate patient monitoring, see **Boxed WARNING**, **WARNINGS**, **Monitoring** subsection of **DOSAGE AND ADMINISTRATION**. The health care practitioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation.

OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (OAA/S)

Assessment Categories				
Responsiveness	Speech	Facial Expression	Eyes	Composite Score
Responds readily to name spoken in normal tone	normal	normal	clear; no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	mild slowing or thickening	mild relaxation	glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	slurring or prominent slowing	marked relaxation (slack jaw)	glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	few recognizable words	——	——	2
Does not respond to mild prodding or shaking	——	——	——	1 (deep sleep)

FREQUENCY OF OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION COMPOSITE SCORES IN ONE STUDY OF CHILDREN UNDERGOING PROCEDURES WITH INTRAVENOUS MIDAZOLAM FOR SEDATION

Age Range (years)	n	OAA/S Score				
		1 (deep sleep)	2	3	4	5 (alert)
1-2	16	6 (38%)	4 (25%)	3 (19%)	3 (19%)	0
>2-5	22	9 (41%)	5 (23%)	8 (36%)	0	0
>5-12	34	1 (3%)	6 (18%)	22 (65%)	5 (15%)	0
>12- 17	18	0	4 (22%)	14 (78%)	0	0
Total (1-17)	90	16 (18%)	19 (21%)	47 (52%)	8 (9%)	0

INTRAMUSCULARLY For sedation/anxiolysis/amnesia

USUAL PEDIATRIC DOSE (NON-NEONATAL)
Sedation after intramuscular midazolam is age and dose dependent; higher doses may result in deeper and more prolonged sedation. Doses of 0.1 to

prior to anesthesia or for procedures, intramuscular midazolam can be used to sedate pediatric patients to facilitate less traumatic insertion of an intravenous catheter for titration of additional medication.	0.15 mg/kg are usually effective and do not prolong emergence from general anesthesia. For more anxious patients, doses up to 0.5 mg/kg have been used. Although not systematically studied, the total dose usually does not exceed 10 mg. If midazolam is given with an opioid, the initial dose of each must be reduced.
INTRAVENOUSLY BY INTERMITTENT INJECTION For sedation/anxiolysis/amnesia prior to and during procedures or prior to anesthesia.	USUAL PEDIATRIC DOSE (NON-NEONATAL) It should be recognized that the depth of sedation/anxiolysis needed for pediatric patients depends on the type of procedure to be performed. For example, simple light sedation/anxiolysis in the preoperative period is quite different from the deep sedation and analgesia required for an endoscopic procedure in a child. For this reason, there is a broad range of dosage. For all pediatric patients, regardless of the indications for sedation/anxiolysis, it is vital to titrate midazolam and other concomitant medications slowly to the desired clinical effect. The initial dose of midazolam should be administered over 2 to 3 minutes. Since midazolam HCl is water soluble, it takes approximately three times longer than diazepam to achieve peak EEG effects; therefore, one must wait an additional 2 to 3 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. If other medications capable of depressing the CNS are coadministered, the peak effect of those concomitant medications must be considered and the dose of midazolam adjusted. The importance of drug titration to effect is vital to the safe sedation/anxiolysis of the pediatric patient. The total dose of midazolam will depend on patient response, the type and duration of the procedure, as well as the type and dose of concomitant medications. 1. *Pediatric patients less than 6 months of age:* Limited information is available in non-intubated pediatric patients less than 6 months of age. It is uncertain when the patient transfers from neonatal physiology to pediatric physiology; therefore, the dosing recommendations are unclear. Pediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation; therefore, titration with small increments to clinical effect and careful monitoring are essential. 2. *Pediatric patients 6 months to 5 years of age:* Initial dose 0.05 to 0.1 mg/kg. A total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint but usually does not exceed 6 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses. 3. *Pediatric patients 6 to 12 years of age:* Initial dose 0.025 to 0.05 mg/kg; total dose up to 0.4 mg/kg may be needed to reach the desired endpoint but usually does not exceed 10 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses. 4. *Pediatric patients 12 to 16 years of age:* Should be dosed as adults. Prolonged sedation may be associated with higher doses; some patients in this age range will require higher than recommended adult doses but the total dose usually does not exceed 10 mg. The dose of midazolam must be reduced in patients premedicated with

	opioid or other sedative agents including midazolam. Higher risk or debilitated patients may require lower dosages whether or not concomitant sedating medications have been administered (see **WARNINGS**).
CONTINUOUS INTRAVENOUS INFUSION For sedation/anxiolysis/amnesia in critical care settings.	USUAL PEDIATRIC DOSE (NON-NEONATAL) To initiate sedation, an intravenous loading dose of 0.05 to 0.2 mg/kg administered over at least 2 to 3 minutes can be used to establish the desired clinical effect IN PATIENTS WHOSE TRACHEA IS INTUBATED. (Midazolam should not be administered as a rapid intravenous dose.) This loading dose may be followed by a continuous intravenous infusion to maintain the effect. An infusion of midazolam has been used in patients whose trachea was intubated but who were allowed to breathe spontaneously. Assisted ventilation is recommended for pediatric patients who are receiving other central nervous system depressant medications such as opioids. Based on pharmacokinetic parameters and reported clinical experience, continuous intravenous infusions of midazolam should be initiated at a rate of 0.06 to 0.12 mg/kg/hr (1 to 2 mcg/kg/min). The rate of infusion can be increased or decreased (generally by 25% of the initial or subsequent infusion rate) as required, or supplemental intravenous doses of midazolam can be administered to increase or maintain the desired effect. Frequent assessment at regular intervals using standard pain/sedation scales is recommended. Drug elimination may be delayed in patients receiving erythromycin and/or other P450-3A4 enzyme inhibitors (see **PRECAUTIONS**: **Drug Interactions**) and in patients with liver dysfunction, low cardiac output (especially those requiring inotropic support), and in neonates. Hypotension may be observed in patients who are critically ill, particularly those receiving opioids and/or when midazolam is rapidly administered. When initiating an infusion with midazolam in hemodynamically compromised patients, the usual loading dose of midazolam should be titrated in small increments and the patient monitored for hemodynamic instability, e.g., hypotension. These patients are also vulnerable to the respiratory depressant effects of midazolam and require careful monitoring of respiratory rate and oxygen saturation.
CONTINUOUS INTRAVENOUS INFUSION For sedation in critical care settings.	USUAL NEONATAL DOSE Based on pharmacokinetic parameters and reported clinical experience in preterm and term neonates WHOSE TRACHEA WAS INTUBATED, continuous intravenous infusions of Midazolam Injection should be initiated at a rate of 0.03 mg/kg/hr (0.5 mcg/kg/min) in neonates <32 weeks and 0.06 mg/kg/hr (1 mcg/kg/min) in neonates >32 weeks. Intravenous loading doses should not be used in neonates, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation. This is particularly important because of the potential for adverse effects related to metabolism of the benzyl alcohol (see **WARNINGS**: **Usage in Preterm Infants and Neonates**). Hypotension may be observed in patients who are critically ill and in preterm and term infants, particularly those receiving fentanyl and/or when midazolam is administered rapidly. Due to an increased risk of apnea, extreme caution is advised when sedating preterm and former preterm patients whose trachea is not intubated.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Midazolam Injection, USP is available in the following:

1 mg/mL midazolam hydrochloride equivalent to 1 mg midazolam/mL
2 mL Vial packaged in 10s (NDC 0641-6057-10) and in 25s (NDC 0641-6057-25)
5 mL Vial packaged in 10s (NDC 0641-6059-10)
10 mL Vial packaged in 10s (NDC 0641-6056-10)

5 mg/mL midazolam hydrochloride equivalent to 5 mg midazolam/mL
1 mL Vial packaged in 10s (NDC 0641-6061-10) and in 25s (NDC 0641-6061-25)
2 mL Vial packaged in 10s (NDC 0641-6063-10) and in 25s (NDC 0641-6063-25)
10 mL Vial packaged in 10s (NDC 0641-6060-10)

STORAGE

Store at 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY

Published studies in animals demonstrate that the use of anesthetic agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of an anesthetic regimen that produced a light surgical plane of anesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with subtle but prolonged cognitive deficits in learning and memory. The clinical significance of these nonclinical findings is not known, and healthcare providers should balance the benefits of appropriate anesthesia in neonates and young children who require procedures against the potential risks suggested by the nonclinical data (See **WARNINGS: Pediatric Neurotoxicity** and **PRECAUTIONS: Pregnancy and Pediatric Use**).

To report SUSPECTED ADVERSE REACTIONS, contact West-Ward Pharmaceuticals Corp. at 1-877-845-0689, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

For Product Inquiry call 1-877-845-0689.

Manufactured by:

WEST-WARD
A HIKMA COMPANY
Eatontown, NJ 07724 USA

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15.5 Triazolam Package Insert

Triazolam tablets, USP CIV

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death *[see Warnings, Drug Interactions]*.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
  Follow patients for signs and symptoms of respiratory depression and sedation.

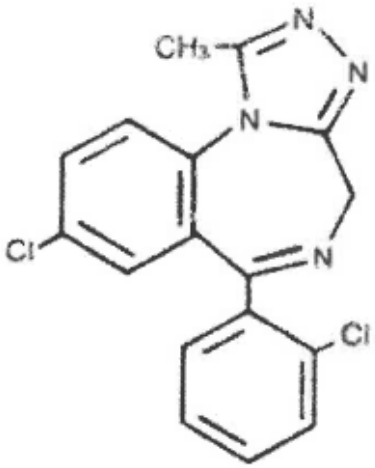
DESCRIPTION

Triazolam is a triazolobenzodiazepine hypnotic agent.

Triazolam is a white crystalline powder, soluble in alcohol and poorly soluble in water. It has a molecular weight of 343.21.

The chemical name for triazolam is 8-chloro-6-(o-chlorophenyl)-1-methyl-4H-s-triazolo-[4,3-α] [1,4] benzodiazepine.

The structural formula is represented below:



Each triazolam tablet, for oral administration, contains 0.125 mg or 0.25 mg of triazolam. Inactive ingredients: **0.125 mg**—cellulose, corn starch, docusate sodium, lactose, magnesium stearate, silicon dioxide, sodium benzoate; **0.25 mg**—cellulose, corn starch, docusate sodium, FD&C Blue No. 2, lactose, magnesium stearate, silicon dioxide, sodium benzoate.

CLINICAL PHARMACOLOGY

Triazolam is a hypnotic with a short mean plasma half-life reported to be in the range of 1.5 to 5.5 hours. In normal subjects treated for 7 days with four times the recommended dosage, there was no

evidence of altered systemic bioavailability, rate of elimination, or accumulation. Peak plasma levels are reached within 2 hours following oral administration. Following recommended doses of triazolam tablets, triazolam peak plasma levels in the range of 1 to 6 ng/mL are seen. The plasma levels achieved are proportional to the dose given.

Triazolam and its metabolites, principally as conjugated glucuronides, which are presumably inactive, are excreted primarily in the urine. Only small amounts of unmetabolized triazolam appear in the urine. The two primary metabolites accounted for 79.9% of urinary excretion. Urinary excretion appeared to be biphasic in its time course.

Triazolam tablets 0.5 mg, in two separate studies, did not affect the prothrombin times or plasma warfarin levels in male volunteers administered sodium warfarin orally.

Extremely high concentrations of triazolam do not displace bilirubin bound to human serum albumin *in vitro*.

Triazolam ^{14}C was administered orally to pregnant mice. Drug-related material appeared uniformly distributed in the fetus with ^{14}C concentrations approximately the same as in the brain of the mother.

In sleep laboratory studies, triazolam tablets significantly decreased sleep latency, increased the duration of sleep, and decreased the number of nocturnal awakenings. After 2 weeks of consecutive nightly administration, the drug's effect on total wake time is decreased, and the values recorded in the last third of the night approach baseline levels. On the first and/or second night after drug discontinuance (first or second post-drug night), total time asleep, percentage of time spent sleeping, and rapidity of falling asleep frequently were significantly less than on baseline (predrug) nights. This effect is often called "rebound" insomnia.

The type and duration of hypnotic effects and the profile of unwanted effects during administration of benzodiazepine drugs may be influenced by the biologic half-life of administered drug and any active metabolites formed. When half-lives are long, the drug or metabolites may accumulate during periods of nightly administration and be associated with impairments of cognitive and motor performance during waking hours; the possibility of interaction with other psychoactive drugs or alcohol will be enhanced. In contrast, if half-lives are short, the drug and metabolites will be cleared before the next dose is ingested, and carry-over effects related to excessive sedation or CNS depression should be minimal or absent. However, during nightly use for an extended period pharmacodynamic tolerance or adaptation to some effects of benzodiazepine hypnotics may develop. If the drug has a short half-life of elimination, it is possible that a relative deficiency of the drug or its active metabolites (ie, in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepine hypnotics: 1) increased wakefulness during the last third of the night and 2) the appearance of increased daytime anxiety after 10 days of continuous treatment.

In a study of elderly (62–83 years old) versus younger subjects (21–41 years old) who received triazolam at the same dose levels (0.125 mg and 0.25 mg), the elderly experienced both greater sedation and impairment of psychomotor performance. These effects resulted largely from higher plasma concentrations of triazolam in the elderly.

INDICATIONS AND USAGE

Triazolam is indicated for the short-term treatment of insomnia (generally 7–10 days). Use for more than 2–3 weeks requires complete reevaluation of the patient (see WARNINGS).

Prescriptions for triazolam should be written for short-term use (7–10 days) and it should not be prescribed in quantities exceeding a 1-month supply.

CONTRAINDICATIONS

Triazolam tablets are contraindicated in patients with known hypersensitivity to this drug or other benzodiazepines.

Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Transplacental distribution has resulted in neonatal CNS depression following the ingestion of therapeutic doses of a benzodiazepine hypnotic during the last weeks of pregnancy.

Triazolam is contraindicated in pregnant women. If there is a likelihood of the patient becoming pregnant while receiving triazolam, she should be warned of the potential risk to the fetus. Patients should be instructed to discontinue the drug prior to becoming pregnant. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered.

Triazolam is contraindicated with medications that significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP 3A) including ketoconazole, itraconazole, nefazodone, and several HIV protease inhibitors, (see WARNINGS and PRECAUTIONS–Drug Interactions).

WARNINGS

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including triazolam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe triazolam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of triazolam than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking triazolam, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when triazolam is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined [see Drug Interactions].

Persistent or Worsening Insomnia

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. **The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.** Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with

sedative-hypnotic drugs. Because some of the important adverse effects of sedative-hypnotics appear to be dose related (see Precautions and Dosage and Administration), it is important to use the smallest possible effective dose, especially in the elderly.

"Sleep-driving" and Other Complex Behaviors

Complex behaviors such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported. These events can occur in sedative-hypnotic-naïve as well as in sedative-hypnotic-experienced persons. Although behaviors such as sleep-driving may occur with sedative-hypnotics alone at therapeutic doses, the use of alcohol and other CNS depressants with sedative-hypnotics appears to increase the risk of such behaviors, as does the use of sedative-hypnotics at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of sedative-hypnotics should be strongly considered for patients who report a "sleep-driving" episode.

Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with sleep-driving, patients usually do not remember these events.

Severe anaphylactic and anaphylactoid reactions

Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including triazolam. Some patients have had additional symptoms such as dyspnea, throat closing, or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with triazolam should not be rechallenged with the drug.

Central nervous system manifestations

An increase in daytime anxiety has been reported for triazolam after as few as 10 days of continuous use. In some patients this may be a manifestation of interdose withdrawal (see CLINICAL PHARMACOLOGY). If increased daytime anxiety is observed during treatment, discontinuation of treatment may be advisable.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of benzodiazepine hypnotics including triazolam. Some of these changes may be characterized by decreased inhibition, eg, aggressiveness and extroversion that seem excessive, similar to that seen with alcohol and other CNS depressants (eg, sedative/hypnotics). Other kinds of behavioral changes have also been reported, for example, bizarre behavior, agitation, hallucinations, depersonalization. In primarily depressed patients, the worsening of depression, including suicidal thinking, has been reported in association with the use of benzodiazepines.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Because of its depressant CNS effects, patients receiving triazolam should be cautioned against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the concomitant ingestion of alcohol and other CNS depressant drugs during treatment with triazolam tablets.

As with some, but not all benzodiazepines, anterograde amnesia of varying severity and paradoxical reactions have been reported following therapeutic doses of triazolam. Data from several sources suggest that anterograde amnesia may occur at a higher rate with triazolam than with other benzodiazepine hypnotics.

Triazolam interaction with drugs that inhibit metabolism via cytochrome P450 3A

The initial step in triazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP 3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of triazolam. Consequently, triazolam should be avoided in patients receiving very potent inhibitors of CYP 3A. With drugs inhibiting CYP 3A to a lesser but still significant degree, triazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with triazolam has been quantified with clinical data; for other drugs, interactions are predicted from *in vitro* data and/or experience with similar drugs in the same pharmacologic class.

The following are examples of drugs known to inhibit the metabolism of triazolam and/or related benzodiazepines, presumably through inhibition of CYP 3A.

Potent CYP 3A inhibitors

Potent inhibitors of CYP 3A that should not be used concomitantly with triazolam include ketoconazole, itraconazole, nefazodone and several HIV protease inhibitors including ritonavir, indinavir, nelfinavir, saquinavir and lopinavir. Although data concerning the effects of azole-type antifungal agents other than ketoconazole and itraconazole on triazolam metabolism are not available, they should be considered potent CYP 3A inhibitors, and their coadministration with triazolam is not recommended (see CONTRAINDICATIONS).

Drugs demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving triazolam (caution and consideration of dose reduction are recommended during coadministration with triazolam)

Macrolide Antibiotics

Coadministration of erythromycin increased the maximum plasma concentration of triazolam by 46%, decreased clearance by 53%, and increased half-life by 35%; caution and consideration of appropriate triazolam dose reduction are recommended. Similar caution should be observed during coadministration with clarithromycin and other macrolide antibiotics.

Cimetidine

Coadministration of cimetidine increased the maximum plasma concentration of triazolam by 51%, decreased clearance by 55%, and increased half-life by 68%; caution and consideration of appropriate triazolam dose reduction are recommended.

Other drugs possibly affecting triazolam metabolism

Other drugs possibly affecting triazolam metabolism by inhibition of CYP 3A are discussed in the PRECAUTIONS section (see PRECAUTIONS–Drug Interactions).

PRECAUTIONS

General

In elderly and/or debilitated patients it is recommended that treatment with triazolam tablets be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination.

Some side effects reported in association with the use of triazolam appear to be dose related. These include drowsiness, dizziness, light-headedness, and amnesia.

The relationship between dose and what may be more serious behavioral phenomena is less certain. Specifically, some evidence, based on spontaneous marketing reports, suggests that confusion, bizarre or abnormal behavior, agitation, and hallucinations may also be dose related, but this evidence is inconclusive. In accordance with good medical practice it is recommended that therapy be initiated at the lowest effective dose (see DOSAGE AND ADMINISTRATION).

Cases of "traveler's amnesia" have been reported by individuals who have taken triazolam to induce sleep while traveling, such as during an airplane flight. In some of these cases, insufficient time was allowed for the sleep period prior to awakening and before beginning activity. Also, the concomitant use of alcohol may have been a factor in some cases.

Caution should be exercised if triazolam is prescribed to patients with signs or symptoms of depression that could be intensified by hypnotic drugs. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional over-dosage is more common in these patients, and the least amount of drug that is feasible should be available to the patient at any one time.

The usual precautions should be observed in patients with impaired renal or hepatic function, chronic pulmonary insufficiency, and sleep apnea. In patients with compromised respiratory function, respiratory depression and apnea have been reported infrequently.

Information for patients

The text of a Medication Guide for patients is included at the end of this insert. To assure safe and effective use of triazolam, the information and instructions provided in this Medication Guide should be discussed with patients.

Risks from Concomitant Use with Opioids

Advise both patients and caregivers about the risks of potentially fatal respiratory depression and sedation when triazolam is used with opioids and not to use such drugs concomitantly unless supervised by a healthcare provider. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined [see Drug Interactions].

"Sleep-driving" and other complex behaviors

There have been reports of people getting out of bed after taking a sedative-hypnotic and driving their cars while not fully awake, often with no memory of the event. If a patient experiences such an episode, it should be reported to his or her doctor immediately, since "sleep-driving" can be dangerous. This behavior is more likely to occur when sedative-hypnotics are taken with alcohol or other central nervous system depressants (see WARNINGS). Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative hypnotic. As with sleep-driving, patients usually do not remember these events.

Laboratory tests

Laboratory tests are not ordinarily required in otherwise healthy patients.

Drug interactions

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and monitor patients closely for respiratory depression and sedation.

Both pharmacodynamic and pharmacokinetic interactions have been reported with benzodiazepines. In particular, triazolam produces additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs which themselves produce CNS depression.

Drugs that inhibit triazolam metabolism via cytochrome P450 3A

The initial step in triazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP 3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of triazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs of this type). Triazolam is contraindicated with ketoconzaole, itraconazole, nefazodone, and several HIV protease inhibitors.

Drugs and other substances demonstrated to be CYP 3A inhibitors of possible clinical significance on the basis of clinical studies involving triazolam (caution is recommended during coadministration with triazolam)

Isoniazid

Coadministration of isoniazid increased the maximum plasma concentration of triazolam by 20%, decreased clearance by 42%, and increased half-life by 31%.

Oral contraceptives

Coadministration of oral contraceptives increased maximum plasma concentration by 6%, decreased clearance by 32%, and increased half-life by 16%.

Grapefruit juice

Coadministration of grapefruit juice increased the maximum plasma concentration of triazolam by 25%, increased the area under the concentration curve by 48%, and increased half-life by 18%.

Drugs demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to triazolam or on the basis of in vitro studies with triazolam or other benzodiazepines (caution is recommended during coadministration with triazolam)

Available data from clinical studies of benzodiazepines other than triazolam suggest a possible drug interaction with triazolam for the following: fluvoxamine, diltiazem, and verapamil. Data from *in vitro* studies of triazolam suggest a possible drug interaction with triazolam for the following: sertraline and paroxetine. Data from *in vitro* studies of benzodiazepines other than triazolam suggest a possible drug interaction with triazolam for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during coadministration of any of these drugs with triazolam (see WARNINGS).

Drugs that affect triazolam pharmacokinetics by other mechanisms

Ranitidine

Coadministration of ranitidine increased the maximum plasma concentration of triazolam by 30%, increased the area under the concentration curve by 27%, and increased half-life by 3.3%. Caution is recommended during coadministration with triazolam.

Carcinogenesis, mutagenesis, impairment of fertility

No evidence of carcinogenic potential was observed in mice during a 24-month study with triazolam in doses up to 4,000 times the human dose.

Pregnancy

1. Teratogenic effects

Pregnancy category X (see CONTRAINDICATIONS).

2. Non-teratogenic effects

It is to be considered that the child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms from the drug, during the postnatal period. Also, neonatal flaccidity has been reported in an infant born of a mother who had been receiving benzodiazepines.

Nursing mothers

Human studies have not been performed; however, studies in rats have indicated that triazolam and its metabolites are secreted in milk. Therefore, administration of triazolam to nursing mothers is not recommended.

Pediatric use

Safety and effectiveness of triazolam in individuals below 18 years of age have not been established.

Geriatric use

The elderly are especially susceptible to the dose related adverse effects of triazolam. They exhibit higher plasma triazolam concentrations due to reduced clearance of the drug as compared with younger subjects at the same dose. To minimize the possibility of development of oversedation, the smallest effective dose should be used (see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Tolerance/Withdrawal Phenomena

Some loss of effectiveness or adaptation to the sleep inducing effects of these medications may develop after nightly use for more than a few weeks and there may be a degree of dependence that develops. For the benzodiazepine sleeping pills that are eliminated quickly from the body, a relative deficiency of the drug may occur at some point in the interval between each night's use. This can lead to (1) increased wakefulness during the last third of the night, and (2) the appearance of increased signs of daytime anxiety or nervousness. These two events have been reported in particular for triazolam.

There can be more severe 'withdrawal' effects when a benzodiazepine sleeping pill is stopped. Such effects can occur after discontinuing these drugs following use for only a week or two, but may be more common and more severe after longer periods of continuous use. One type of withdrawal phenomenon is the occurrence of what is known as 'rebound insomnia'. That is, on the first few nights after the drug is stopped, insomnia is actually worse than before the sleeping pill was given. Other withdrawal

phenomena following abrupt stopping of benzodiazepine sleeping pills range from mild unpleasant feelings to a major withdrawal syndrome which may include abdominal and muscle cramps, vomiting, sweating, tremor, and rarely, convulsions.

ADVERSE REACTIONS

During placebo-controlled clinical studies in which 1,003 patients received triazolam tablets, the most troublesome side effects were extensions of the pharmacologic activity of triazolam, eg, drowsiness, dizziness, or light-headedness.

The figures cited below are estimates of untoward clinical event incidence among subjects who participated in the relatively short duration (i.e., 1 to 42 days) placebo-controlled clinical trials of triazolam. The figures cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those in clinical trials. These figures cannot be compared with those obtained from other clinical studies involving related drug products and placebo, as each group of drug trials is conducted under a different set of conditions.

Comparison of the cited figures, however, can provide the prescriber with some basis for estimating the relative contributions of drug and nondrug factors to the untoward event incidence rate in the population studied. Even this use must be approached cautiously, as a drug may relieve a symptom in one patient while inducing it in others. (For example, an anticholinergic, anxiolytic drug may relieve dry mouth [a sign of anxiety] in some subjects but induce it [an untoward event] in others.)

	Triazolam	PLACEBO
Number of Patients	**1003**	**997**
% Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Light-headedness	4.9	0.9
Coordination disorders/ataxia	4.6	0.8
Gastrointestinal		
Nausea/vomiting	4.6	3.7

In addition to the relatively common (i.e., 1% or greater) untoward events enumerated above, the following adverse events have been reported less frequently (i.e., 0.9% to0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

In addition to these untoward events for which estimates of incidence are available, the following adverse events have been reported in association with the use of triazolam and other benzodiazepines: amnestic symptoms (anterograde amnesia with appropriate or inappropriate behavior), confusional states (disorientation, derealization, depersonalization, and/or clouding of consciousness), dystonia, anorexia,

fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention. Other factors may contribute to some of these reactions, eg, concomitant intake of alcohol or other drugs, sleep deprivation, an abnormal premorbid state, etc.

Other events reported include: paradoxical reactions such as stimulation, mania, an agitational state (restlessness, irritability, and excitation), increased muscle spasticity, sleep disturbances, hallucinations, delusions, aggressiveness, falling, somnambulism, syncope, inappropriate behavior and other adverse behavioral effects. Should these occur, use of the drug should be discontinued.

The following events have also been reported: chest pain, burning tongue/glossitis/stomatitis.

Laboratory analyses were performed on all patients participating in the clinical program for triazolam. The following incidences of abnormalities were observed in patients receiving triazolam and the corresponding placebo group. None of these changes were considered to be of physiological significance.

	Triazolam		PLACEBO	
Number of Patients	**380**		**361**	
% of Patients Reporting:	**Low**	**High**	**Low**	**High**
Hematology				
Hematocrit	*	*	*	*
Hemoglobin	*	*	*	*
Total WBC count	1.7	2.1	*	1.3
Neutrophil count	1.5	1.5	3.3	1.0
Lymphocyte count	2.3	4.0	3.1	3.8
Monocyte count	3.6	*	4.4	1.5
Eosinophil count	10.2	3.2	9.8	3.4
Basophil count	1.7	2.1	*	1.8
Urinalysis				
Albumin	—	1.1	—	*
Sugar	—	*	—	*
RBC/HPF	—	2.9	—	2.9
WBC/HPF	—	11.7	—	7.9
Blood chemistry				
Creatinine	2.4	1.9	3.6	1.5
Bilirubin	*	1.5	1.0	*
SGOT	*	5.3	*	4.5
Alkaline phosphatase	*	2.2	*	2.6

* Less than 1%

When treatment with triazolam is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during therapy with triazolam and are of no known significance.

DRUG ABUSE AND DEPENDENCE

Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Tolerance may occur to both the desired and undesired effects of drugs and may develop at different rates for different effects.

Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

Controlled Substance

Triazolam is a controlled substance under the Controlled Substance Act, and triazolam tablets have been assigned to Schedule IV.

Abuse, Dependence and Withdrawal

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting, sweating, dysphoria, perceptual disturbances and insomnia), have occurred following abrupt discontinuance of benzodiazepines, including triazolam. The more severe symptoms are usually associated with higher dosages and longer usage, although patients at therapeutic dosages given for as few as 1–2 weeks can also have withdrawal symptoms and in some patients there may be withdrawal symptoms (daytime anxiety, agitation) between nightly doses (see CLINICAL PHARMACOLOGY). Consequently, abrupt discontinuation should be avoided and a gradual dosage tapering schedule is recommended in any patient taking more than the lowest dose for more than a few weeks. The recommendation for tapering is particularly important in any patient with a history of seizure.

The risk of dependence is increased in patients with a history of alcoholism, drug abuse, or in patients with marked personality disorders. Such dependence-prone individuals should be under careful surveillance when receiving triazolam. As with all hypnotics, repeat prescriptions should be limited to those who are under medical supervision.

OVERDOSAGE

Because of the potency of triazolam, some manifestations of overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg).

Manifestations of overdosage with triazolam tablets include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiratory depression and apnea have been reported with overdosages of triazolam. Seizures have occasionally been reported after overdosages.

Death has been reported in association with overdoses of triazolam by itself, as it has with other benzodiazepines. In addition, fatalities have been reported in patients who have overdosed with a combination of a single benzodiazepine, including triazolam, and alcohol; benzodiazepine and alcohol

levels seen in some of these cases have been lower than those usually associated with reports of fatality with either substance alone.

As in all cases of drug overdosage, respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. An adequate airway should be maintained. Intravenous fluids may be administered.

Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS should be consulted prior to use.

Experiments in animals have indicated that cardiopulmonary collapse can occur with massive intravenous doses of triazolam. This could be reversed with positive mechanical respiration and the intravenous infusion of norepinephrine bitartrate or metaraminol bitartrate. Hemodialysis and forced diuresis are probably of little value. As with the management of intentional overdosage with any drug, the physician should bear in mind that multiple agents may have been ingested by the patient.

The oral LD_{50} in mice is greater than 1,000 mg/kg and in rats is greater than 5,000 mg/kg.

DOSAGE AND ADMINISTRATION

It is important to individualize the dosage of triazolam tablets for maximum beneficial effect and to help avoid significant adverse effects.

The recommended dose for most adults is 0.25 mg before retiring. A dose of 0.125 mg may be found to be sufficient for some patients (e.g., low body weight). A dose of 0.5 mg should be used only for exceptional patients who do not respond adequately to a trial of a lower dose since the risk of several adverse reactions increases with the size of the dose administered. A dose of 0.5 mg should not be exceeded.

In geriatric and/or debilitated patients the recommended dosage range is 0.125 mg to 0.25 mg. Therapy should be initiated at 0.125 mg in these groups and the 0.25 mg dose should be used only for exceptional patients who do not respond to a trial of the lower dose. A dose of 0.25 mg should not be exceeded in these patients.

As with all medications, the lowest effective dose should be used.

HOW SUPPLIED

Triazolam tablets are available in the following strengths and package sizes:

0.125 mg (white, imprinted G3717):

Bottles of 10	NDC 59762-3717-4
Bottles of 100	NDC 59762-3717-9

0.25 mg (powder blue, scored, imprinted G3718):

Bottles of 10	NDC 59762-3718-4
Bottles of 100	NDC 59762-3718-9
Bottles of 500	NDC 59762-3718-3

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

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Peapack, NJ 07977

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MEDICATION GUIDE
TRIAZOLAM Tablets, C-IV

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

- **Triazolam is a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma and death.**
- After taking triazolam, you may get up out of bed while not being fully awake and do an activity that you do not know you are doing. The next morning, you may not remember that you did anything during the night. You have a higher chance for doing these activities if you drink alcohol or take other medicines that make you sleepy with triazolam. Reported activities include:
  - driving a car ("sleep-driving")
  - making and eating food
  - talking on the phone
  - having sex
  - sleep-walking

  Call your healthcare provider right away if you find out that you have done any of the above activities after taking triazolam.
- Do not take triazolam unless you are able to stay in bed a full night (7 to 8 hours) before you must be active again.
- Do not take more triazolam than prescribed.

What is triazolam?

- Triazolam is a prescription medicine used to treat certain types of insomnia including difficulty falling asleep, waking up often during the night, or waking up early in the morning.

Rx only

MEDICATION GUIDE
TRIAZOLAM Tablets, C-IV

- **Triazolam is a federal controlled substance (C-IV) because it can be abused or lead to dependence.** Keep triazolam in a safe place to prevent misuse and abuse. Selling or giving away triazolam may harm others, and is against the law. Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.
- It is not known if triazolam is safe and effective in children.
- Elderly patients are especially susceptible to dose related adverse effects when taking triazolam.
- It is not known if triazolam is safe and effective for use longer than 2 to 3 weeks.

Do not take triazolam if you:

- are allergic to triazolam, other benzodiazepines, or any of the ingredients in triazolam. See the end of this Medication Guide for a complete list of ingredients in triazolam.
- take antifungal medicines including ketoconazole and itraconazole
- take a medicine to treat depression called nefazodone
- take medicines to treat HIV infection called protease inhibitors, including ritonavir, indinavir, nelfinavir, saquinavir or lopinavir

Before you take triazolam, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of depression, mental illness or, suicidal thoughts
- have a history of drug or alcohol abuse or addiction
- have kidney or liver disease
- have lung disease, breathing problems, or sleep apnea
- are pregnant or plan to become pregnant. Triazolam may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if triazolam can pass through your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take triazolam.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Do not take triazolam with other medicines that can make you sleepy. Taking triazolam with certain other medicines can cause side effects or affect how well triazolam or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

How should I take triazolam?

- See "What is the most important information I should know about triazolam?"
- Take triazolam exactly as your healthcare provider tells you to take it.
- Take triazolam right before you get into bed. Or you can take triazolam after you have been in bed and have trouble falling asleep.
- Do not take triazolam with or right after a meal.
- Do not take triazolam unless you are able to get a full night's sleep before you must be active again.
- If you take too much triazolam, get emergency treatment right away

Rx only

MEDICATION GUIDE
TRIAZOLAM Tablets, C-IV

What should I avoid while taking triazolam?

- Do not drive, operate machinery, do other dangerous activities or do anything that needs you to be alert until you know how triazolam affects you.
- You should not drink alcohol while you are taking triazolam.

What are the possible side effects of triazolam?
Triazolam may cause serious side effects, including:

- See "What is the most important information I should know about triazolam?"
- **Other conditions.** Call your healthcare provider if your insomnia worsens or is not better within 7 to 10 days. This may mean that there is another condition causing your sleep problem.
- **Abnormal thoughts and behavior.** Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, and suicidal thoughts or actions.
- **Withdrawal symptoms.** You may have withdrawal symptoms for 1 to 2 days when you stop taking triazolam suddenly. Withdrawal symptoms include trouble sleeping, unpleasant feelings, stomach and muscle cramps, vomiting, sweating, shakiness, and seizures. Talk to your healthcare provider about slowly stopping triazolam to avoid withdrawal symptoms.
- **Abuse and dependence.** Taking triazolam can cause physical and psychological dependence. Physical and psychological dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.
- **Memory loss, including "traveler's amnesia"**
- **Anxiety**
- **Severe allergic reactions.** Symptoms include swelling of the tongue or throat, trouble breathing, nausea and vomiting. Get emergency medical help if you have these symptoms after taking triazolam.

The most common side effects of triazolam include:

- drowsiness
- dizziness
- "pins and needles" feeling on your skin
- headache
- lightheadedness
- difficulty with coordination

You may still feel drowsy the next day after taking triazolam. **Do not drive or do other dangerous activities (including operating machinery) after taking triazolam until you feel fully awake.**
These are not all the possible side effects of triazolam. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store triazolam?

- Store at room temperature between 68°F to 77° F (20°C to 25°C).
- Protect from light.
- **Keep triazolam and all medicines out of the reach of children**
- **Do not use triazolam after the expiration date on the bottle.**

Rx only

MEDICATION GUIDE
TRIAZOLAM Tablets, C-IV

General information about the safe and effective use of triazolam.

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- Do not use triazolam for a condition for which it was not prescribed.
- Do not give triazolam to other people, even if they have the same symptoms that you have. It may harm them.
- You can ask your healthcare provider or pharmacist for information about triazolam that is written for healthcare professionals.

What are the ingredients in triazolam?
Active Ingredient: triazolam
Inactive Ingredients: 0.125 mg tablet: cellulose, corn starch, docusate sodium, lactose, magnesium stearate, silicon dioxide, sodium benzoate, 0.25 mg tablet: cellulose, corn starch, docusate sodium, FD&C Blue No. 2, lactose, magnesium stearate, silicon dioxide, sodium benzoate.

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

This product's label may have been updated. For current full prescribing information, please visit www.greenstonellc.com.

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15.6 Delirium Questionnaire (Sample)

Instructions to the patient: Please answer all of the questions independently to the best of your ability.

1. Have you ever experienced delirium after surgery or a procedure?
   - □ Yes
   - □ No

If you answered question 1 as "yes", you have completed this questionnaire. Otherwise, continue to question 2.

2. Have you ever been diagnosed with dementia?
   - □ Yes
   - □ No

3. Have you ever been diagnosed with any of the following? If so, please check all that apply.

☐ Depression	☐ Liver failure
☐ Hypotension (Low blood pressure)	☐ Stroke
☐ Alcoholism/substance abuse	☐ Kidney failure

4. Are you able to complete you daily activities independently?
   - □ Yes
   - □ No

5. Are you able to get everywhere you need to by yourself during the day?
   - □ Yes
   - □ No

You have now completed your portion of the questionnaire Thank you for your participation with this important research.

To be Completed by Research Staff

1. Does the patient take any of the following medications? If so, please list all that apply.

   a. Opiods:_____
   b. Anticonvulsants:_____
   c. Benzodiazepines:_____
   d. Anticholinergics:_____
   e. Antipsychotics:_____

15.7 Satisfaction Surveys

15.7.1 Post-Surgery Anesthesiologist/CRNA Satisfaction Survey (Sample)

Post-Surgery Anesthesiologist/CRNA Survey

Instructions for the survey: Please select the response you feel best describes the statement based on this subject's surgical procedure.

1. The patient's pain level was well controlled

☐Disagree very much ☐Disagree ☐Disagree a little ☐Agree a little ☐Agree ☐Agree very much

2. The patient's anxiety level was well controlled

☐Disagree very much ☐Disagree ☐Disagree a little ☐Agree a little ☐Agree ☐Agree very much

3. Intravenous (IV) medication was required for breakthrough pain during surgery

☐Disagree very much ☐Disagree ☐Disagree a little ☐Agree a little ☐Agree ☐Agree very much

4. There was no undesired movement

☐Disagree very much ☐Disagree ☐Disagree a little ☐Agree a little ☐Agree ☐Agree very much

5. The patient was cooperative

☐Disagree very much ☐Disagree ☐Disagree a little ☐Agree a little ☐Agree ☐Agree very much

7. There was no operative deviation or complication as a result of the patients initial anesthesia medication

☐Disagree very much ☐Disagree ☐Disagree a little ☐Agree a little ☐Agree ☐Agree very much

Type of complication/deviation (if any):_____

Research Staff Use Only:

Study ID#: _____

Date of surgery: _____

Ophthalmology surgeon: _____

Date of survey completion: _____

Name of survey administrator: _____

15.7.2 Post Surgery Surgeon Satisfaction Survey (Sample)

Post-Surgery Surgeon Survey

Instructions for the survey: Please select the response you feel best describes the statement based on this subject's surgical procedure.

Surgery Group Type (please select one): ☐Cataract ☐Retina ☐Cornea ☐Glaucoma

Type of Local Anesthesia (please select one): ☐Topical ☐Subconjunctival ☐Subtenon's ☐ Retrobulbar/peribulbar ☐ Other

1. I was satisfied with the anesthesia administered during surgery

□Disagree very much	□Disagree	□Disagree a little	□Agree a little	□Agree	□Agree very much

2. The patient's pain level was well controlled

□Disagree very much	□Disagree	□Disagree a little	□Agree a little	□Agree	□Agree very much

3. The patient's anxiety level was well controlled

□Disagree very much	□Disagree	□Disagree a little	□Agree a little	□Agree	□Agree very much

4. There was no undesired movement

□Disagree very much	□Disagree	□Disagree a little	□Agree a little	□Agree	□Agree very much

5. The patient was cooperative

□Disagree very much	□Disagree	□Disagree a little	□Agree a little	□Agree	□Agree very much

8. There was no deviation from the operative standard that occurred as a result of the patient's initial anesthesia medication

□Disagree very much	□Disagree	□Disagree a little	□Agree a little	□Agree	□Agree very much

Type of complication/deviation (if any): _____

7. Did you need to request additional pain medications from the anesthesiologist?
   - □ Yes
   - □ No

Research Staff Use Only:
Study ID#: _____
Date of surgery: _____
Ophthalmology surgeon: _____
Date of survey completion: _____
Name of survey administrator: _____

15.7.3 Post-Surgery Patient Satisfaction Survey (Sample)

Instructions for the survey: Please complete this survey independently without the help of your family members or friends. We want to know about your personal experience.

When answering each question below, check the box next to the response you feel best describes the statement. There is no right or wrong answer.

1. I hurt during surgery

☐Disagree very much	☐Disagree	☐Disagree a little	☐Agree a little	☐Agree	☐Agree very much

2. I felt good during surgery

☐Disagree very much	☐Disagree	☐Disagree a little	☐Agree a little	☐Agree	☐Agree very much

3. I felt pain during surgery

☐Disagree very much	☐Disagree	☐Disagree a little	☐Agree a little	☐Agree	☐Agree very much

4. I was satisfied with the anesthesia care (relaxing medication) during surgery

☐Disagree very much	☐Disagree	☐Disagree a little	☐Agree a little	☐Agree	☐Agree very much

5. I itched during surgery

☐Disagree very much	☐Disagree	☐Disagree a little	☐Agree a little	☐Agree	☐Agree very much

6. I felt relaxed during surgery

☐Disagree very much	☐Disagree	☐Disagree a little	☐Agree a little	☐Agree	☐Agree very much

7. I felt safe during surgery

☐Disagree very much	☐Disagree	☐Disagree a little	☐Agree a little	☐Agree	☐Agree very much

8. I threw up after surgery

☐Disagree very much ☐Disagree ☐Disagree a little ☐Agree a little ☐Agree ☐Agree very much

9. I felt like throwing up after surgery

☐Disagree very much ☐Disagree ☐Disagree a little ☐Agree a little ☐Agree ☐Agree very much

10. I would have the same anesthetic (relaxing medication) again

☐Disagree very much ☐Disagree ☐Disagree a little ☐Agree a little ☐Agree ☐Agree very much

11. I was too hot or cold during surgery

☐Disagree very much ☐Disagree ☐Disagree a little ☐Agree a little ☐Agree ☐Agree very much

12. My pain level was as expected and well controlled during the surgery

☐Disagree very much ☐Disagree ☐Disagree a little ☐Agree a little ☐Agree ☐Agree very much

13. During your operation, your anesthesiologist gave you a medication to make you feel more calm, relaxed and/or sleepy. If you were to have this type of surgery again, would you prefer:

☐More medicine ☐Same medicine ☐Less medicine ☐No medicine

Research Staff Use Only:

Study ID#: _____

Date of surgery: _____

Ophthalmology surgeon: _____

Date of survey completion: _____

Name of survey administrator: _____

15.8 AE, SAE, and UP Tracking and Reports

15.8.1 AE, SAE, and UP Report Log (Sample)

AE/SAE/UP Report Log

This log tracks assessment and reporting of internal AEs. AEs should be assessed for seriousness, severity, whether or not they are expected, and whether they are related. From this information, a determination of expedited reporting can be made. Events that are serious (OR pose a greater risk of harm than was previously known or recognized), at least possibly related to the research, and unexpected are Unanticipated Problems (UPs) and must be reported within two days to the BUMC IRB. Other events (non-UPs) should be reported to the IRB at the time of the progress report.

To be Completed by Designated Study Staff			To be Completed by Study PI								To be Completed by Designated Study Staff
Subject ID #	AE Date	AE description	SAE?[1]	Relationship with study intervention	Expected?	Severity Grade[2]	UP?[3]	Intervention Administered	Ongoing or Resolved with Date	Initial and Date of Review	IRB reporting (expedited for UPs, vs. progress report)
			☐ yes ☐ no	☐ definite ☐ probable ☐ possible ☐ unlikely ☐ unrelated	☐ expected ☐ unexpected	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐ yes ☐ no		☐ ongoing ☐ resolved Resolution Date: ________	Initial: ________ Date: ________	☐ UP reporting date: ________ ☐ Progress report
			☐ yes ☐ no	☐ definite ☐ probable ☐ possible ☐ unlikely ☐ unrelated	☐ expected ☐ unexpected	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐ yes ☐ no		☐ ongoing ☐ resolved Resolution Date: ________	Initial: ________ Date: ________	☐ UP reporting date: ________ ☐ Progress report
			☐ yes ☐ no	☐ definite ☐ probable ☐ possible ☐ unlikely ☐ unrelated	☐ expected ☐ unexpected	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐ yes ☐ no		☐ ongoing ☐ resolved Resolution Date: ________	Initial: ________ Date: ________	☐ UP reporting date: ________ ☐ Progress report
			☐ yes ☐ no	☐ definite ☐ probable ☐ possible ☐ unlikely ☐ unrelated	☐ expected ☐ unexpected	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐ yes ☐ no		☐ ongoing ☐ resolved Resolution Date: ________	Initial: ________ Date: ________	☐ UP reporting date: ________ ☐ Progress report

[1]SAE Classification: AE is an SAE if it meets any of the criteria below.		[2]Severity Grade		[3]Unanticipated problem: If AE meets all three criteria below report to IRB within 2 days.
- Results in death - Life threatening - Requires/prolongs hospitalization	- Results in disability or incapacity - Congenital Anomaly/birth defect - Medically important event	1 - Mild AE (not requiring treatment) 2 - Moderate AE (resolved with treatment) 3 - Severe (inability to carry on normal activities/required professional medical attention)	4 - Severe: life threatening or disabling AE 5 - Death	- Unexpected - Related/possibly related to the research - Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

15.8.2 AE, SAE, and UP Review Log (Sample)

AE/SAE/UP Review Log

This log tracks assessment and reporting of internal AEs. AEs should be assessed for seriousness, severity, whether or not they are expected, and whether they are related. From this information, a determination of expedited reporting can be made. Events that are serious (OR pose a greater risk of harm than was previously known or recognized), at least possibly related to the research, and unexpected are Unanticipated Problems (UPs) and must be reported within two days to the BUMC IRB. Other events (non-UPs) should be reported to the IRB at the time of the progress report.

To be Completed by Designated Study Staff			To be Completed by PI and Safety Monitor				Was the event reviewed and reported within the protocol timeline? *If no, write a comment*	Comments
Subject ID #	AE Date	AE description	Signature of PI	Date of PI Review	Signature of Safety Monitor	Date of Safety Monitor Review		
							☐ yes ☐ no	
							☐ yes ☐ no	
							☐ yes ☐ no	
							☐ yes ☐ no	
							☐ yes ☐ no	

15.8.3 SAE and UP Report Form (Sample)

Designated Study Personnel Completing and Reviewing this Report		
Printed Name of Designated Individual(s) Completing this Report	**Signature of Designated Individual(s) Completing this Report**	**Date**
1.		
2.		
3.		
4.		
5.		
Printed Name of PI	**Signature of PI**	**Date**
Printed Name of Safety Monitor	**Signature of Safety Monitor**	**Date**

Subject Information						
Type of Event	**Date of Birth**	**Age (at time of event)**	**Sex**	**Height**	**Weight**	**BMI**
☐ Serious Adverse Event ☐ Unanticipated Problem			☐ Male ☐ Female	☐ Inches ☐ cm	☐ lbs ☐ kg	

SAE/UP Information						
AE Diagnosis	**Date and Time of Onset**	**Date and Time at End of Event**	**Was the event related to the study intervention**	**Severity Grade**	**SAE Criteria**	**Outcome**
			☐ definite ☐ probable ☐ possible ☐ unlikely ☐ unrelated	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐ death ☐ life threatening ☐ new or prolonged hospitalization Admission date: _____ Discharge Date: _____ ☐ congenital anomaly/birth defect ☐ significant disability/incapacity ☐ important medical event	☐ recovered/resolved ☐ recovered/resolved with sequelae ☐ recovering/resolving ☐ not recovered/not resolved ☐ fatal Date: _____ ☐ unknown

Investigational Product						
Study Medication and Dosage (mg)		**Name of Administrator**	**Administration Date and Time**	**Administered per Protocol**	**If No, Comment**	**Event Associated with Medical Error**
Oral	*Intravenous*					
☐ triazolam ☐ 0.125 mg ☐ 0.25 mg ☐ placebo ☐ 1 capsule ☐ 2 capsules	☐ midazolam ☐ 1.0 mg ☐ 2.0 mg ☐ placebo ☐ 1.0 mg equivalent ☐ 2.0 mg equivalent			☐ Yes ☐ No		☐ Yes ☐ No

Relevant Medical History			
Medical Condition or Event	**Ongoing or Resolved**	**Onset Date**	**End Date**
1.	☐ Ongoing ☐ Resolved		
2.	☐ Ongoing ☐ Resolved		
3.	☐ Ongoing ☐ Resolved		
4.	☐ Ongoing ☐ Resolved		
5.	☐ Ongoing ☐ Resolved		
6.	☐ Ongoing ☐ Resolved		
7.	☐ Ongoing ☐ Resolved		
8.	☐ Ongoing ☐ Resolved		

Relevant Laboratory/Imaging Tests			
Test	**Date of Test**	**Result of Test**	**Normal or Abnormal**
1.			☐ Normal ☐ Abnormal
2.			☐ Normal ☐ Abnormal
3.			☐ Normal ☐ Abnormal
4.			☐ Normal ☐ Abnormal
5.			☐ Normal ☐ Abnormal

Concomitant Medications						
Drug Name	**Start Date**	**Stop Date**	**Dose**	**Frequency**	**Route/Location**	**Indication**
1.						
2.						
3.						
4.						
5.						
6.						
7.						
8.						
9.						

Adverse Event Information	
Event description: **Include course of the event, signs/symptoms, diagnostic test results, therapeutic measures for the event, etc.**	
Relatedness Assessment: **Record a brief reason for the PI's assigned causality**	

15.8.4 Data Safety Monitoring Report (Sample)

Independent Data Monitoring Committee (DMC) Recommendation Letter

Date: _____

Meeting Participants:

Dr. Stephen P Christiansen, *Professor and Chairman Department of Ophthalmology*

Dr. Gheorghe Doros, *Professor of Biostatistician*

The DMC, charged with the review of safety data for the Protocol number H-36590, reviewed data summaries based on a data cut-off date of _____.

As a result, the IDMC recommends:

[ ] To continue trial unmodified until next scheduled or triggered meeting.

[ ] To continue trial unmodified, and advance the next review.

[ ] To continue trial unmodified, and request additional expert review/analyses.

[ ] Describe and provide timelines of additional review:

[ ] To continue trial and amend protocol as described:

Provide description:

[ ] To pause enrollment pending resolution of the following issue:

Specify issue:

[ ] To set up a meeting with SC to discuss continuation of the trial.

[ ] To stop the trial for the following reasons:

Specify reason(s):

General Comments:

1.

2.

3.

4.

5.

Specific Recommendations:

A.

B.

C.

D.

E.

The next DMC meeting will be held in _____. Date and time to be determined.

Respectfully Submitted,

_____ _____

Date Stephen P Christiansen, MD

Professor and Chair