

**COVER PAGE**

**PROTOCOL**

November 3, 2017

Rev. 1.0

NCT03178942

A Randomized, Double-Blind, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Permethrin Cream, 5% (Encube Ethicals) Compared to Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc.) in the Treatment of Scabies

Protocol Number: 71675502  
Novum Study Number: 71675502

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A Randomized, Double-Blind, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Permethrin Cream, 5% (Encube Ethicals) Compared to Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc.) in the Treatment of Scabies

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**1.0 TITLE PAGE**

<b>Study Title</b>	A Randomized, Double-Blind, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Permethrin Cream, 5% (Encube Ethicals) Compared to Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc.) in the Treatment of Scabies
<b>Drug Product</b>	Permethrin Cream, 5%
<b>Population</b>	Approximately 250 patients, 2 years of age and older with clinically documented evidence of infestation with <i>Sarcoptes scabiei</i> (scabies)
<b>Study Design</b>	Randomized, double-blind, parallel-design, multiple-site bioequivalence study with clinical endpoints
<b>Sponsor</b>	Encube Ethicals
<b>Protocol/Study Number</b>	71675502
<b>Protocol Date</b>	11/03/2017

**NIIRB**  
**November 14, 2017**  
**APPROVED**

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A Randomized, Double-Blind, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Permethrin Cream, 5% (Encube Ethicals) Compared to Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc.) in the Treatment of Scabies

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### 2.0 KEY STUDY PERSONNEL AND FACILITIES

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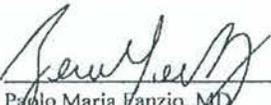
A Randomized, Double-Blind, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Permethrin Cream, 5% (Encube Ethicals) Compared to Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc.) in the Treatment of Scabies

**3.0 SIGNATURE PAGE**

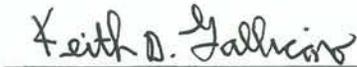
We, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study. The study will be performed according to this protocol, all applicable Food and Drug Administration (FDA) regulations, International Conference on Harmonisation (ICH) guidelines and Good Clinical Practice (GCP) standards.

  
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**PRINCIPAL INVESTIGATOR'S SIGNATURE**

I \_\_\_\_\_, agree to conduct protocol 71675502 Rev 1 in accordance with FDA regulations, ICH guidelines and GCP. I understand that no deviations from the protocol may be made without the prior permission of the Sponsor (Encube Ethicals) or Novum Pharmaceutical Research Services, the company managing the study.

\_\_\_\_\_  
Principal Investigator

\_\_\_\_\_  
Date

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### 5.0 SYNOPSIS

<b>Protocol Number</b>	71675502
<b>Title</b>	A Randomized, Double-Blind, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Permethrin Cream 5% (Encube Ethicals) Compared to Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc.) in the Treatment of Scabies
<b>Objectives</b>	<p>The objectives of this study are to:</p> <ol style="list-style-type: none"><li>1. Evaluate the therapeutic equivalence of the Test formulation, Permethrin Cream, 5% (Encube Ethicals) to the marketed product, Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc.) in patients with scabies.</li><li>2. Compare the safety of Test and Reference treatments in patients with scabies.</li></ol>
<b>Sponsor</b>	Encube Ethicals
<b>Study Products</b>	<ul style="list-style-type: none"><li>• <b>Test:</b> Permethrin Cream, 5% (Encube Ethicals)</li><li>• <b>Reference:</b> Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc.)</li></ul> Study products will be supplied in tubes (60 grams).
<b>Dosage Regimen</b>	Patients will administer a single dose of study product on the day of Visit 1 (i.e., Day 1). A second application may be required if evidence of scabies infestation is microscopically demonstrated (i.e., living mites, viable mite eggs, or mite fecal matter) are present on Visit 2 (Day 14 ± 4). Each patient will receive up to two applications.
<b>Route of Administration</b>	Topical
<b>Treatment Randomization</b>	1:1 (Test: Reference)
<b>Patient Population</b>	Approximately 250 patients, 2 years of age and older with clinically documented evidence of active infestation with <i>Sarcoptes scabiei</i> (scabies).
<b>Study Design</b>	Randomized, double-blind, parallel-group, multiple-site bioequivalence study with clinical endpoints
<b>Study Conduct</b>	<p>Eligible patients will be randomized in a 1:1 ratio to one of the two treatments (Test or Reference) at Visit 1. Patients will administer a single application of study product on the day of Visit 1 (i.e., Day 1). A second application may be required if presence of active scabies infestation is microscopically demonstrated (i.e., living mites, viable mite eggs, or mite fecal matter present) on Visit 2 (Day 14 ± 4). Patients will complete three clinic visits as follows:</p> <ul style="list-style-type: none"><li>• Visit 1 (Day 1): Screening/Baseline</li></ul>

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	<ul style="list-style-type: none"><li>• Visit 2 (Day 14 ± 4): Interim Visit</li><li>• Visit 3 (Day 28 ± 4): End of Study Or Early Termination</li></ul> <p>Final assessments will be carried out at Visit 3 (Day 28 ± 4), which is the test-of-cure visit. Therapeutic cure of scabies will be evaluated based on microscopic evidence of absence of scabies infestation (i.e., no living mites, no viable mite eggs, and no mite fecal matter), visual evidence of absence of new lesions and healing of original lesions, regardless of the presence of post-scabetic nodules (i.e., post-scabetic nodules need not be considered as new lesions or persistence of old lesions).</p>
<b>Inclusion Criteria</b>	<ol style="list-style-type: none"><li>1. Male or non-pregnant, non-lactating female, 2 years of age or older.</li><li>2. If female and of childbearing potential, prepared to abstain from sexual intercourse or use a reliable method of contraception during the study (e.g., double barrier methods, IUD, oral, transdermal or injected hormonal contraceptives). Female patients using hormonal contraceptives should have been on the same product/dosing regimen for at least 28 days before baseline and should not change this regimen during the study.</li><li>3. Signed informed consent that meets all criteria of current FDA and ICH regulations. For patients who are considered minors in the state the study is being conducted (&lt; 18 years in most states) the parent or legal guardian should sign the consent form and the child will be required to sign a patient “assent” form, as appropriate. Patients 11-17 years of age will read and sign an IRB-approved assent form and patients 6-10 years of age will provide verbal assent. Patients 2-5 years of age will be exempt from providing assent based on the child’s comprehension and cognitive skills.</li><li>4. Clinical diagnosis of active scabies by presence of a burrow and/or typical scabetic lesions at the classic sites of infestation.</li><li>5. Parasitological confirmation of clinical diagnosis with demonstration under light microscope of mites and/or their products (larvae, eggs or fecal material).</li><li>6. Symptom score of 2 or 3 on a 4-point rating scale of 0-3 for nocturnal itching/pruritus.</li><li>7. Ability to apply or have study product applied as directed. If patient is a child, then parent/guardian will apply study product to him/her.</li></ol>
<b>Exclusion Criteria</b>	<ol style="list-style-type: none"><li>1. Patients who are pregnant, lactating, or planning to become pregnant during the study.</li><li>2. Any systemic or dermatologic disorder that, in the opinion of the Investigator, will interfere with the study results or increase the risk of adverse events (AEs).</li><li>3. Known hypersensitivity to permethrin cream or any of its components,</li></ol>

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	<p>ragweed or chrysanthemums, synthetic pyrethroids or pyrethrin.</p> <ol style="list-style-type: none"><li>4. Use of any systemic or topical acaricide or ectoparasiticide within one month before Screening.</li><li>5. Patient has signs of a systemic infection or is receiving systemic therapy for an infectious disease.</li><li>6. Patients with severe cutaneous bacterial or fungal infections requiring therapy (including systemic and topical antibiotics) or coexisting dermatological disorder that could interfere with the diagnosis and subsequent monitoring of scabies) or heavily crusted with lesions consistent with Norwegian scabies.</li><li>7. Patients with an underlying immunodeficient state (including prolonged treatment with corticosteroids), immunosuppressive disorders requiring therapy, severe systemic disease and history of HIV infection.</li><li>8. Any condition, medical, psychological, or social, that, in the Investigator’s opinion, would interfere with participation in the study.</li><li>9. Family members of employees of the clinic or Investigator.</li><li>10. Patients who, in the opinion of the Investigator, would be non-compliant with the requirements of the study protocol.</li><li>11. Patients whose close personal contacts will not or are not willing to comply with standard of care for Scabies management.</li><li>12. Receipt of any drug as part of a research study within 30 days before Screening.</li><li>13. History of seizures.</li><li>14. Use of systemic corticosteroids within two weeks before Screening.</li><li>15. Use of topical corticosteroids within one week before Screening.</li><li>16. Previous participation in this study.</li></ol>
<b>Efficacy Endpoint</b>	<p>The primary efficacy endpoint is the proportion of patients in each treatment group with Therapeutic Cure (parasitological cure plus clinical cure) of scabies at the test-of-cure visit conducted at Day 28 ± 4. A parasitological cure is defined as failure to demonstrate microscopically the presence of scabies infestation (i.e., no living mites, no viable mite eggs, and no mite fecal matter present). A clinical cure is defined as visual evidence of absence of new lesions and healing of original lesions, regardless the presence of post-scabietic nodules (i.e., post-scabietic nodules need not be considered as new lesions or persistence of old lesions).</p>
<b>Evaluation of Therapeutic Equivalence</b>	<p><u>Primary Analysis:</u></p> <p>Therapeutic equivalence of the Test product to the Reference product based on the primary endpoint will be evaluated in the per-protocol (PP) population. If the 90% confidence interval on the absolute difference between the proportion of patients who are considered a Therapeutic Cure (primary) in the Test and Reference groups is contained within the range [-20%, +20%] then</p>

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	<p>therapeutic equivalence of the Test product to the Reference product will be considered to have been demonstrated.</p> <p><u>Supportive Analyses:</u></p> <p>The following supportive analyses will be performed for the primary endpoint:</p> <ol style="list-style-type: none"><li>1. The primary analysis will be performed including patients who completed Visit 2 within <math>14 \pm 2</math> days and Visit 3 within <math>28 \pm 4</math> days.</li><li>2. The primary analysis will be performed including patients who completed Visit 2 within <math>14 \pm 2</math> days and Visit 3 between Day 26 and Day 32, inclusive.</li><li>3. The primary analysis will be performed including patients who completed Visit 2 within <math>14 \pm 2</math> days and Visit 3 within <math>28 \pm 2</math> days.</li></ol> <p>To declare therapeutic equivalence of the Test product to the Reference product, therapeutic equivalence must be demonstrated for only the primary analysis.</p> <p><b><u>Treatment-by-Site Interaction and Pooling of Clinical Sites</u></b></p> <p>As this is a multiple-site study, the interaction of treatment-by-site may be evaluated for the primary efficacy endpoint in the PP population (for equivalence testing). The treatment-by-site interaction will be evaluated by the Breslow-Day test for homogeneity of the odds ratio at the 5% significance level (<math>p &lt; 0.05</math>). A site(s) with a low enrollment rate(s) may be pooled with its geographically closest site, so as to avoid bias in the estimation of a treatment-by-site interaction effect. The pooling will be done for low enrolling sites that account for less than 4-7% of the total number of patients in the PP population at the site with the highest enrolling rate in the PP population. If the treatment-by-site interaction term is found to be statistically significant (<math>p &lt; 0.05</math>) for the primary endpoint, then the interaction term will also be assessed for clinical relevance before pooling the data across sites. This will include examination of Therapeutic Cure rates at each site where sample sizes per treatment may be influential in the assessment of the interaction.</p>
<b>Safety Analysis</b>	<p>Adverse events will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 20.0 or higher and summarized by treatment group. Summary tables comparing the type, incidence, date of onset, date of resolution, severity, action taken, outcome and Investigator’s opinion of relationship to the study product will be prepared by treatment group. If sufficient data exist, AE frequencies will be compared between treatments using Fisher’s exact test or a similar test.</p> <p>Signs and symptoms of scabies will not be considered AEs, unless in the Investigator’s opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers that it is in the patient’s best interest to be dropped from continued participation in the study and</p>

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	<p>given alternative therapy for their condition.</p> <p>Concomitant medication use during the study will be tabulated by patient and by treatment.</p> <p>All patients who are randomized to the active treatment period of the study who received study product will be included in the comparative safety analysis.</p>
<b>Sample Size Determination</b>	<p>For the primary endpoint analysis (proportion of patients in the PP population who are considered to be a Therapeutic Cure on Day 28 ± 4), sample size is estimated for therapeutic equivalence of the Test to the Reference product.</p> <p>Based on data from a previous bioequivalence study conducted to support approval of the first generic product of permethrin cream, 5%, the Therapeutic Cure rate (<math>p_R</math>) of the Reference product (Elimite™ permethrin cream 5%) is expected to be about 88% in the PP population. Assuming that the Therapeutic Cure rate for the Test group (<math>p_T</math>) is an absolute difference of 5% lower than the Therapeutic Cure rate for the Reference group (i.e., <math>p_T - p_R = -5\%</math>), a sample size of 107 patients in each active group in PP population will provide at least 90% power to demonstrate therapeutic equivalence (i.e., the 90% confidence interval [Yates' continuity-corrected] on <math>p_T - p_R</math> is within a defined equivalence range [-20% to +20%]).</p> <p>To allow for approximately 14% of patients who may drop out from the study or are otherwise non-evaluable, approximately 250 patients (125 in each treatment group) will be randomized, such that there will be an estimated 214 patients (107 per group) in the PP population for statistical evaluation of therapeutic equivalence.</p>

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**6.0 STUDY SCHEMATIC**

	<b>Visit 1</b> Screening/Baseline (Day 1)	<b>Visit 2</b> Interim Visit (Day 14 ± 4)	<b>Visit 3</b> (Day 28 ± 4) End of Study or Early Termination
Informed Consent	X		
Medical history and Baseline Demographics	X		
Vital Signs	X		X
Adverse Events	X	X	X
Concomitant Medications	X	X	X
Microscopic Examination	X	X	X
Scabies Signs and Symptoms Rating (pruritus, lesion count)	X	X	X
Urine Pregnancy Test	X		X
Review Inclusion/Exclusion Criteria	X		
Collect and Review Diary		X	X
Provide Diary	X	X	
Dispense Study Product	X	X*	
Collect and Weigh Study Product		X	X*

\*If retreatment is necessary, the originally dispensed (i.e., at Visit 1) study product will be dispensed at Visit 2 and collected at Visit 3.

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### 7.0 LIST OF ABBREVIATIONS AND TERMS

ADaM	Analysis Dataset Model
AE	Adverse Event
ANDA	Abbreviated New Drug Application
ANOVA	Analysis of variance
C	Celsius
CDISC	Clinical Data Interchange Consortium
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
eCTD	Electronic Common Technical Document
F	Fahrenheit
FDA	Food & Drug Administration
GCP	Good Clinical Practices
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IUD	Intrauterine Device
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
OGD	Office of Generic Drugs
OTC	Over-the-Counter
PP	Per-Protocol
RLD	Reference Listed Drug
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
USA	United States of America

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### 8.0 INTRODUCTION

#### 8.1 Disease Being Treated

Scabies is an infestation of the skin by the human itch mite (*Sarcoptes scabiei*). The microscopic scabies mite burrows into the upper layer of the skin where it lives and lays its eggs. The most common signs and symptoms of scabies are intense itching, skin rash and the presence of tiny burrows caused by the female mites tunneling through the superficial surface of the skin. The scabies mite is spread by direct, prolonged, skin-to-skin contact with infected persons.<sup>1,2</sup>

As of 2010, scabies affects approximately 100 million people (1.5% of the world population) and is equally common in both sexes. Scabies is found worldwide and affects people of all races and social classes. Scabies outbreaks are common in crowded public places, nursing homes, extended-care facilities, prisons and child care facilities.<sup>1,2</sup>

Initial infections require 4-6 weeks to become symptomatic. Re-infection, however, may manifest symptoms within as few as 24 hours. Scabies symptoms are allergic, exhibiting a delay in onset as well as relief after the parasites have been eradicated. A more severe form of infection is crusted scabies, formerly known as Norwegian scabies, which is often associated with immunosuppression.<sup>1,2</sup>

Diagnosis of scabies is made based on clinical symptoms, such as nocturnal itching and appearance and distribution of the rash. Definitive diagnosis includes the microscopic identification of the mite, mite eggs, or mite fecal matter in the skin. This can be done by carefully removing a mite or skin scraping from the end of its burrow (or near a lesion) using the tip of a needle and observing under a microscope.<sup>1,2</sup>

#### 8.2 Availability and Efficacy of Already Approved Therapies

Food & Drug Administration (FDA)-approved scabies therapies, called scabicides are available only by prescription. Such treatments include topical medications such as permethrin cream 5% (Elimite™), crotamiton lotion/cream 10% (Eurax®, Crotan®) and lindane lotion 1%. Oral anti-parasitic therapy includes ivermectin (Stromectol®), which is considered effective in combination with topical therapy.<sup>1,2</sup>

Permethrin, a pyrethroid, is active against a broad range of pests including lice, ticks, fleas, mites, and other arthropods. It acts on the nerve cell membrane to disrupt the sodium channel current by which the polarization of the membrane is regulated. Delayed repolarization and paralysis of the pests are the consequences of this disturbance.

Permethrin is considered the drug of choice for the treatment of scabies. It is safe for use in adults and children 2 months and older. One or two applications, about a week apart may be necessary to eliminate all mites and eggs on the patient's body.<sup>1,2</sup>

#### 8.3 Scientific and Statistical Considerations

Permethrin is rapidly metabolized by ester hydrolysis to inactive metabolites which are excreted primarily in the urine. Although the amount of permethrin absorbed after a single application of the 5% cream has not been determined precisely, data from studies with 14C-labeled permethrin and

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absorption studies of the cream applied to patients with moderate to severe scabies indicate it is 2% or less of the amount applied. As the systemic absorption of the Reference product, Elimite™ cream (permethrin) 5% is extremely low, its relevance to clinical activity is not significant.<sup>3</sup> A therapeutic efficacy evaluation based on relief from scabies symptoms and eradication of living mites in the skin after using study products is considered the most appropriate methodology for this study.<sup>4,5</sup>

A previous bioequivalence study conducted for the FDA marketing approval for the first generic product of permethrin cream, 5% indicated that the rate of clinical cure for this product and that for the Reference product, Elimite™ cream (permethrin) 5%, was about 88%; there was no placebo treatment arm in that study.<sup>6</sup>

The design and sample size estimation for the study described in this protocol are based on a previous bioequivalence study.

The FDA published a Draft Guidance on Permethrin Cream in October 2017,<sup>7</sup> which was after the start of the conduct of study 71675502 (last patient, last visit occurred on October 30, 2017). Therefore, this protocol was revised to accommodate recommendations in that Guidance, as appropriate. Key revisions are the following:

1. Revised definition of the per-protocol (PP) population to include those patients that are treatment failures on Day 14 as Therapeutic Failures in the final analysis (see section 11.3.1).
2. Revised definition of the Safety population (see section 11.3.2).
3. Removed the secondary efficacy endpoint (see section 11.5).
4. Removed the Yates' continuity correction for calculation of 90% confidence intervals on the absolute difference between the proportion of patients who are considered a Therapeutic Cure in the Test and Reference groups (see section 11.6).
5. Added three supportive analyses to evaluate different evaluation windows for Visit 2 (Day 14) and Visit 3 (Day 28) (see section 11.6).
6. Added descriptive statistics for the number and frequency of re-infestations from Day 14 (Therapeutic Cure) to Day 28 (Therapeutic Failure) in the PP population.

The Guidance recommends a  $\pm 2$ -day window for both the Day 14 and Day 28 visits. This protocol incorporates a  $\pm 4$ -day window for both visits. The justification for the wider visit window is that permethrin cream 5% is expected to cure scabies infestation after a single treatment. That is, if it works by Day 14 it should still work by Day 28, and thus the re-infestation rate from Day 14 to Day 28 is expected to be low. Therefore, a wider visit window on Day 28 should be acceptable. The effect of different visit window durations at Day 14 and Day 28 will be explored in the three supportive analyses.

The Guidance also recommends that the youngest patient (with scabies infestation who meets the inclusion criteria) from each household is considered to be the index or primary patient of the household for evaluation of the primary endpoint, that other members of the household and close contacts are enrolled as secondary patients (not included in primary endpoint analysis) and evaluated for all safety parameters, and that secondary patients should receive the same study treatment as the

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index patient. This protocol did not define an index patient and secondary patients from each household. Instead all eligible household members that qualified for the study were separately randomized to receive study product (Test or Reference) and included in the primary endpoint analysis. The justification for this design is that there is no placebo treatment arm in this study; therefore, there is minimal chance that household members would exchange or share treatments, given that each enrolled member would receive active treatment. Because the risk of treatment exchange or sharing within a household is higher when some members receive active treatment and others receive placebo treatment, the Guidance-recommendation that primary and secondary subjects within a household all receive the same study treatment is necessary for a placebo-controlled study but is not necessary for an active-treatment-only study.

#### 9.0 STUDY OBJECTIVES

The objectives of this study are to:

1. Evaluate the therapeutic equivalence of the Test formulation, Permethrin Cream, 5% (Encube Ethicals) to the marketed product, Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc.) in patients with scabies.
2. Compare the safety of Test and Reference treatments in patients with scabies.

#### 10.0 INVESTIGATIONAL PLAN

##### 10.1 Study Design and Plan Description

This randomized, double-blind, parallel-design, multiple-site study is designed to evaluate the therapeutic efficacy and safety of a generic Permethrin Cream, 5% (Encube Ethicals) compared to the FDA Reference Listed Drug (RLD), Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc.) in patients with scabies.

Before any study-specific procedures are performed, all patients will read and sign the IRB-approved informed consent that meets all criteria of current FDA and International Conference of Harmonisation (ICH) regulations. For patients who are considered minors in the state the study is being conducted (< 18 years in most states) the parent or legal guardian should sign the consent form and the child will be required to sign a patient “assent” form, as appropriate. Patients 11-17 years of age will read and sign an IRB-approved assent form and patients 6-10 years of age will provide verbal assent. Patients 2-5 years of age will be exempt from providing assent based on the child’s comprehension and cognitive skills.

Approximately 250 eligible patients, 2 years of age and older with a clinical diagnosis of active scabies based on signs and symptoms and confirmation of microscopic evidence of scabies mites in the skin will be randomized in a 1:1 ratio (Test: Reference) to one of the two study products as follows:

- **Test:** Permethrin Cream, 5%, (Encube Ethicals)
- **Reference:** Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc. \*)

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(\*Note: The RLD used to conduct the bioequivalence studies is Elimate™ (permethrin) topical cream (5%) (NDC Code 40076-230-60) manufactured by DPT Laboratories LTD., San Antonio TX 78215 and Manufactured for Prestium Pharma Inc. Although the RLD labeling indicates that the product is manufactured for Prestium Pharma Inc., please note that Prestium Pharma Inc., Newtown PA 18940 was acquired by Mylan Pharmaceuticals Inc., which is also the NDA holder of the RLD. This is consistent with the information verified in the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations.)

Patients will be instructed to self-administer a single dose of study product or, if patient is a child, then parent/guardian will apply study product to him/her on Day 1 according to the dosing instructions provided. A second application may be required if presence of scabies infestation is microscopically demonstrated (i.e., living mites, viable mite eggs, or mite fecal matter present) at Visit 2. The second dose will be self-administered by the patient or if patient is a child, then parent/guardian will apply study product to him/her on the evening of Visit 2. Eligible household members and close contacts of the patient who were in need of treatment will be offered generic permethrin cream as a method to reduce cross-contamination within a household. Additionally, household members will be requested to follow the standard hygiene practices. Patients whose household members are not willing to comply with the standard of care for Scabies management (i.e., use of generic permethrin cream and standard hygiene practices) will not be enrolled in the study.

During the study, patients will visit the clinical center for a total of three scheduled visits:

- Visit 1 (Day 1): Screening/Baseline
- Visit 2 (Day 14 ± 4): Interim Visit
- Visit 3 (Day 28 ± 4): End of Study or Early Termination

Final assessments will be carried out at Visit 3 (Day 28 ± 4), which is the test-of-cure visit. The test-of-cure visit will occur 4 weeks (± 4 days) after the end of the single application treatment on study Day 1 or 2 weeks (± 4 days) after the end of a second application, if necessary, on Day 14 ± 4. Therapeutic cure of scabies will be evaluated based on microscopic evidence of absence of scabies infestation (i.e., no living mites, no viable mite eggs, and no mite fecal matter), visual evidence of absence of new lesions, and healing of original lesions, regardless of the presence of post-scabetic nodules (i.e., post-scabetic nodules need not be considered as new lesions or persistence of old lesions). The primary statistical analysis of interest is the proportion of patients in each treatment group with Therapeutic Cure (parasitological cure plus clinical cure) of scabies

#### 10.2 Selection of Study Design

This study has been designed based on information provided in the Summary Basis for Approval of permethrin cream, 5% (Alpharma, U.S. Pharmaceuticals Division) and prescription information for the Reference product, Elimate™ cream (permethrin) 5%.<sup>6</sup>

Statistical analyses of the clinical data will be based on recommendations in FDA Guidances.<sup>5,7-10</sup> Details of the analyses will be outlined within the Statistical Analysis Plan (SAP).

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### 10.3 Selection of Study Population

#### 10.3.1 Inclusion Criteria

1. Male or non-pregnant, non-lactating female, 2 years of age or older.
2. If female and of childbearing potential, prepared to abstain from sexual intercourse or use a reliable method of contraception during the study (e.g., double barrier method, IUD, oral, transdermal or injected hormonal contraceptives). Female patients using hormonal contraceptives should have been on the same product/dosing regimen for at least 28 days before baseline and should not change this regimen during the study.
3. Signed informed consent that meets all criteria of current FDA and ICH regulations. For patients who are considered minors in the state the study is being conducted (< 18 years in most states) the parent or legal guardian should sign the consent form and the child will be required to sign a patient “assent” form, as appropriate. Patients 11-17 years of age will read and sign an IRB-approved assent form and patients 6-10 years of age will provide verbal assent. Patients 2-5 years of age will be exempt from providing assent based on the child’s comprehension and cognitive skills.
4. Clinical diagnosis of active scabies by presence of a burrow and/or typical scabietic lesions at the classic sites of infestation.
5. Parasitological confirmation of clinical diagnosis with demonstration under light microscope of mites and/or their products (larvae, eggs or fecal material).
6. Symptom score of 2 or 3 on a 4-point rating scale of 0-3 for nocturnal itching/pruritus.
7. Ability to apply or have study product applied as directed. If patient is a child, then parent/guardian will apply study product to him/her

#### 10.3.2 Exclusion Criteria

1. Patients who are pregnant, lactating, or planning to become pregnant during the study.
2. Any systemic or dermatologic disorder that, in the opinion of the Investigator, will interfere with the study results or increase the risk of adverse events (AEs).
3. Known hypersensitivity to permethrin cream or any of its components, ragweed or chrysanthemums, synthetic pyrethroids or pyrethrin.
4. Use of any systemic or topical acaricide or ectoparasiticide within one month before Screening.
5. Patient has signs of a systemic infection or is receiving systemic therapy for an infectious disease.
6. Patients with severe cutaneous bacterial or fungal infections requiring therapy (including systemic and topical antibiotics) or coexisting dermatological disorder that could interfere with the diagnosis and subsequent monitoring of scabies) or heavily crusted with lesions consistent with Norwegian scabies.

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7. Patients with an underlying immunodeficient state (including prolonged treatment with corticosteroids), immunosuppressive disorders requiring therapy, severe systemic disease and history of HIV infection.
8. Any condition, medical, psychological, or social, that, in the Investigator's opinion, would interfere with participation in the study.
9. Family members of employees of the clinic or Investigator.
10. Patients who, in the opinion of the Investigator, would be non-compliant with the requirements of the study protocol.
11. Patients whose close personal contacts will not or are not willing to comply with standard of care for Scabies management.
12. Receipt of any drug as part of a research study within 30 days before Screening.
13. History of seizures.
14. Use of systemic corticosteroids within two weeks before Screening.
15. Use of topical corticosteroids within one week before Screening.
16. Previous participation in this study.

### 10.3.3 Restrictions During the Study

Patients will be instructed to refrain from the following treatments throughout the study:

- Any other prescription/over-the-counter (OTC)/natural/herbal scabicides.
- Systemic and topical corticosteroids or immunosuppressants (e.g., high dose of systemic corticosteroids, systemic calcineurin inhibitors, Azathioprine).
- Prolonged exposure to sunlight/UV, use of tanning beds, chemical treatments/peels, dermabrasion or any dermatological procedures that will potentially influence or hinder the evaluation of scabies signs and symptoms.

Note: Use of antibiotics (systemic and topical) for cutaneous bacterial infections during the conduct of the study will be allowed after the Screening/Baseline visit, but the usage should be restricted to the Principal Investigator's discretion in cases of secondary infections of scabietic lesions. The usage of the antibiotic should be included on the concomitant medication page.

### 10.3.4 Removal of Patients from the Study

Patients will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the Investigator may withdraw a patient from the study to protect the health of that patient. A patient may also be withdrawn for not complying with study procedures. The clinical report will include all reasons for early withdrawals.

Reasons for removal may include, but are not limited to the following:

- Patient withdrew consent

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- Significant AE that led the Investigator or patient to withdraw for safety reasons
- Non-compliance with protocol including the use of restricted medication
- Pregnancy
- Significant worsening of scabies such that the Investigator and/or patient believes it is in the best interest of the patient to withdraw from the study and be provided alternative treatment
- Participant enrolls in another clinical trial, or is found to have previously enrolled in this study

### 10.3.5 Early Terminations

If a randomized patient terminates from the study early, all efforts will be made to complete the End of Study procedures. For early termination the Investigator will fully document the reason for early termination.

## 10.4 Treatments

### 10.4.1 Treatment Administration

Patients will be provided with verbal and written instructions on how to administer the study product. Eligible household members and close contacts of the patient will be offered permethrin cream (if they are in need of treatment) and will follow the appropriate application and decontamination instructions as follows. Patients whose household members are not willing to comply with the standard of care for Scabies management (i.e., use of generic permethrin cream and standard hygiene practices) will not be enrolled in the study.

Patients will be instructed to thoroughly massage study product into (clean) skin from the head to the soles of the feet, including all folds, interdigital space, groin, navel, and external genitalia, as well as the skin under nails and jewelry (i.e., rings, watches). Scabies rarely infests the scalp of adults, although the hairline, neck, temple, and forehead may be infested in infants and geriatric patients. Usually 30 grams is sufficient for an average adult. Patients must NOT wash their hands from the time the product is applied until the time the product is removed. Study product should be reapplied if hands are washed after application. Scabies rarely infests the scalp of adults, although the hairline, neck, temple, and forehead may be infested in toddlers and geriatric patients. For toddlers, only the following areas on the head should be treated: the scalp, temple, and forehead, avoiding the eyes, because transmission of mites may potentially occur during breastfeeding. Clean clothing should be worn after product application. The cream should be removed by washing (shower or bath) after 8 to 14 hours. Contact with eyes during application must be avoided. Eyes should be flushed with water immediately if the study product gets in the eyes.

On Day 1, before applying treatment, all bedding, clothing, and towels used by infested persons or their household, sexual, and close contacts should be decontaminated by washing in hot water and drying in a hot dryer, by dry-cleaning, or by sealing in a plastic bag for at least 72 hours.

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Instructions on good hygiene and proper methods of decontamination will be provided to the patient.

Patients may experience persistent pruritus after treatment. This is not to be considered a sign of treatment failure and is not an indication for retreatment. Demonstrable living mites (i.e., living mites, viable mite eggs, or mite fecal matter) on at Visit 2 indicate that re-treatment is necessary. Retreatment should occur the evening of Visit 2.

Standard anti-itch medication (oral hydroxyzine capsule or oral solution) will be provided by the Investigator, as deemed necessary based on his/her judgment, for the relief of intolerable itching, or to facilitate nighttime sleep during the treatment period (when the itching severely affects sleep). Frequent use of the anti-itch medication is not encouraged. Suggested dosing for patients > 12 years old is 25 mg per os every 6-8 hours as needed or at hora somni; the maximum dosage allowed is 100 mg/24 h. For patients ≥ 2 years old is 2 mg/kg/day per os divided every 6-8 hours as needed; the maximum dosage allowed is 50 mg/24 h. Patients will be required to record the use (date, time and dose) of rescue medication in the patient diary.

Skin sores that become infected may be treated with an appropriate antibiotic provided by the Investigator if such decision is made based on the clinical picture and at the discretion of the Investigator.

#### 10.4.2 Identity of Investigational Product

The following products will be used in the study:

- **Test:** Permethrin Cream, 5% (Encube Ethicals)
- **Reference:** Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc.\*)

#### 10.4.3 Study Product Shipment, Storage, and Retention

The study product will be shipped to each Investigator's Site from a centralized pharmacy. The Principal Investigator at each site is responsible for ensuring that all study products are stored in a locked, secure location, with access limited to the Investigator and his/her designee(s). An accurate inventory of the study product will be maintained in accordance with federal regulations.

Study product will be stored at controlled room temperature 20-25°C (68-77°F) [USP Controlled Room Temperature]. Any excursions from the permitted range of 15-30°C (59-86°F) will require prompt notification to Novum, and thereafter Novum will notify the Sponsor.

For every study product shipment received at the site, the Investigator (or designee) will randomly select at least one block of study product for retention. The selection process will ensure a sufficient amount of retention samples are retained as per Sponsor requirement (i.e., amount needed for 5x release testing). Each kit in the block selected for retention will be labeled as a retention sample and should not be dispensed to study patients. The selected retention samples will be retained by each site under FDA regulations as study retention samples.<sup>11</sup>

Once the site has been notified that they may do so, all unused study product and empty or partially used tubes of study product, other than that randomly selected for retention samples will

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be returned to the Sponsor or designee. It is important that retention samples not be returned to Novum, the Sponsor or the packaging company during or at the end of the study.

#### 10.4.4 Method of Assigning Patients to Treatment Groups

The study product will be randomized, packaged and blinded by an independent packaging company. Randomization will be pre-planned according to a computer-generated randomization schedule. All randomized study products will be blinded and packaged in sealed boxes. Each block will contain two patients' worth of product (1 Test and 1 Reference). Each patient kit will include 1 x 60 gram tube of study product, which should be sufficient for full treatment.

The randomization number will be a unique four-digit number. Patient numbers will be assigned immediately before dispensing of study product and in ascending sequential order, beginning with the lowest available number at the study site. Each patient kit and each dispensed study tube should include the four-digit patient number on the label.

At the end of the study, after all the clinical data have been entered and the study database has been locked, a copy of the randomization schedule will be sent to the statistician.

#### 10.4.5 Study Blind

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the patient assignment. Each study site will have at least one Independent Dispenser. The role of the Independent Dispenser is to dispense and collect study product to/from the patients, maintain dispensing records, and ensure the study product logs are complete and accurate. The patient will be requested not to discuss the appearance of the study product with the Investigator or study staff.

A perforated or two-part label will be attached to the study product supplies for each patient. One part of the label will remain attached to the box. This part should include the following information:

- Protocol number
- Randomization number
- Space for patient's initials
- Caution New Drug limited by federal law to investigational use
- Space for dispensing date, storage information, general directions and the Sponsor's name

The other part will be removed before dispensing and attached to patient's source documentation.

To ensure information that could potentially bias handling of data is not disclosed, the clinical packaging company will hold the randomization scheme until database lock. For each patient the tear off portion of the label will have a concealed scratch off area describing the assigned treatment, to be unblinded only in the case of medical emergency and should be kept at the site with the study documents when the study is completed.

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Whenever possible, the Novum Medical Monitor must be contacted before breaking the blind for any patient.

At the end of the study, after the database has been locked, each site will be sent a sealed envelope containing the full study randomization that should be retained with the study documents in the event of an FDA inspection.

### 10.4.6 Compliance

Patients will be provided with a diary to record the time and date of dosing, concomitant medications and AEs. Use of restricted medications will be reviewed based on patient diary entry(s) and verbal discussion with the patient. Dosing compliance will be checked based on the dosing diary entry and verbal discussion with the patient at Visits 2 and 3 (when applicable). Patients will be considered compliant with dosing if they administer 100% of the required number of doses (i.e., one or, if necessary, two doses).

## 10.5 Study Conduct

### 10.5.1 Visit 1 (Day 1): Screening/Baseline

1. **Informed Consent:** Patients should sign informed consent that meets all criteria of current FDA regulations. For patients who are considered minors in the state the study is being conducted (< 18 years in most states) the parent or legal guardian should sign the consent form and the child will be required to sign a patient “assent” form, as appropriate. Patients 11-17 years of age will read and sign an IRB-approved assent form and patients 6-10 years of age will provide verbal assent. Patients 2-5 years of age will be exempt from providing assent based on the child’s comprehension and cognitive skills.
2. **Medical History and Baseline Demographics:** Review the patient’s demographic and medical history within the last six months.
3. **Vital Signs:** Record Patient’s blood pressure, pulse, temperature and respiration rate.
4. **Adverse Events:** Patients will be questioned about any changes in patient’s health status, including occurrence of AEs since signing the ICF or Assent or AEs that may have occurred during the visit. All AEs will be recorded.
5. **Concomitant Medications:** Review the patient’s use of current and prior medication use over the previous 6 months.
6. **Microscopic Examination:** Skin scrapings will be taken to assess microscopic evidence of scabies mites/eggs/feces in the skin. Refer to Appendix B.
7. **Scabies Signs and Symptoms Rating (pruritus, lesion count):** Patients will be asked to complete a rating scale to record symptom severity of nocturnal itching/pruritus. Investigators will be asked to complete a rating scale to record severity of lesion count infestation. Refer to Appendix A
8. **Pregnancy Test:** Women of childbearing potential will take a urine pregnancy test.

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9. **Review Inclusion/Exclusion Criteria:** Confirm the patient meets all inclusion/exclusion criteria.
10. **Provide Dosing Diary:** Patients will receive a diary to record date and time of dosing and duration of application, AEs and concomitant medications.
11. **Dispense Study Product:** Eligible patients will receive randomized study product with instructions for dosing at home.

### 10.5.2 Visit 2 (Day 14 ± 4): Interim Visit

1. **Adverse Events:** Patients will be questioned about any health status changes/AEs since last visit. All AEs will be recorded.
2. **Concomitant Medication:** Review the patient's use of any new or ongoing concomitant medications since the last visit.
3. **Microscopic Examination:** Skin scrapings will be taken to record microscopic evidence of scabies mites/eggs/feces in the skin. Refer to Appendix B.
4. **Scabies Signs and Symptoms Rating (pruritus, lesion count):** Patients will be asked to complete a rating scale to record symptom severity of nocturnal itching. Investigators will be asked to complete a rating scale to record severity of lesion count infestation. Refer to Appendix A
5. **Collect and Review Patient Diary:** Collect previously dispensed diary and review for compliance with the protocol.
6. **Provide Patient Diary:** Patients will receive a diary to record any changes in health status (AEs), and concomitant medication.
7. **Collect and Weigh Study Product:** Collect and weigh used study product tubes. The weight of the used study will be recorded in the drug accountability log. Patients who do not require a second application will return the used study product tube. Patients deemed eligible by the Investigator for a second application (based on presence of living mites by microscopic examination at Visit 2) will keep study product, and apply a second dose at home.

### 10.5.3 Visit 3 (Day 28 ± 4): End of Study or Early Termination

1. **Vital Signs:** Record Patient's blood pressure, pulse, temperature and respiration rate.
2. **Adverse Events:** Patients will be questioned about any health status changes/AEs since last visit. All AEs will be recorded.
3. **Concomitant Medication:** Review the patient's use of any new or ongoing concomitant medications since the last visit.
4. **Microscopic Examination:** Skin scrapings will be taken to record microscopic evidence of scabies mites/eggs/feces in the skin. Refer to Appendix B.
5. **Scabies Signs and Symptoms Rating (pruritus, lesion count):** Patients will be asked to complete a rating scale to record symptom severity of nocturnal itching. Investigators will be

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- asked to complete a rating scale to record severity of lesion count infestation. Refer to Appendix A
6. **Pregnancy Test:** A pregnancy test will be required of all female patients of childbearing potential.
  7. **Collect and Review Patient Diary:** Collect previously dispensed diary and review for compliance with the protocol.
  8. **Collect and Weigh Study Product:** Collect and weigh used study product tubes (in cases when re-treatment was required or if the patient inadvertently did not return the study product at Visit 2). The weight of the used study tube will be recorded in the drug accountability log.
  9. Review completeness of all source documents and discharge from the study.

### 10.6 Study Procedures

#### 10.6.1 Informed Consent

At Visit 1, before performing any study-related procedures, patients should sign informed consent that meets all criteria of current FDA regulations. For patients who are considered minors in the state the study is being conducted (< 18 years in most states) the parent or legal guardian should sign the consent form and the child will be required to sign a patient “assent” form, as appropriate. Patients 11-17 years of age will read and sign an IRB-approved assent form and patients 6-10 years of age will provide verbal assent. Patients 2-5 years of age will be exempt from providing assent based on the child’s comprehension and cognitive skills.

#### 10.6.2 Medical History and Demographics

At Visit 1, each patient will be required to provide basic demographic information: date of birth, gender, ethnicity and race. Patients will also be questioned about medical history, including acute and chronic medical history and medical history relevant to their scabies.

#### 10.6.3 Vital Signs

At Visit 1 and at the end of the study (Visit 3 or early study termination as appropriate), sitting blood pressure, pulse, respiration rate and temperature will be recorded.

#### 10.6.4 Adverse Events

At Visit 1, patients will be questioned about any changes in patient’s health status, including occurrence of AEs since signing the ICF or Assent or AEs that may have occurred during the visit. All AEs will be recorded. At Visits 2 and 3 patients will be questioned regarding any changes in their medical status since their previous visit. Any changes will be reported as AEs.

#### 10.6.5 Concomitant Medication

At Visit 1, patients will be questioned about current and prior medication use over the previous 6 months. At Visits 2 and 3 patients will be questioned about ongoing or any new concomitant medication use.

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### 10.6.6 Microscopic Examination

At each clinic visit, the Investigator will conduct a dermatological examination to identify living mites in the skin. A dermoscope can be used (but is not required) to observe lesions/papules/blisters/burrows on the skin. Once determined that the lesions are characteristic of scabies, the Investigator will collect a skin scraping sample for identification of living mites/eggs/feces by light microscopy. See Appendix B for details.<sup>12-14</sup>

### 10.6.7 Scabies Signs and Symptoms Rating

At each clinic visit, patients will be asked to rate the severity of nocturnal pruritus using a 4-point scale for pruritus severity. Investigators will be asked to complete a rating scale to record severity of lesion count infestation (Appendix A).<sup>15</sup>

### 10.6.8 Pregnancy Test

All females of childbearing potential will have a urine pregnancy test performed at Visits 1 and 3. The test must be negative at Visit 1 for the patient to be eligible for inclusion in the study. If the patient is of non-childbearing potential, the source document must list the reason why she is of non-childbearing potential (e.g., postmenopausal).

Any patient who becomes pregnant during the study must be discontinued and End of Study procedures completed. The outcome of the pregnancy will be followed by the Investigator to birth or early termination as appropriate. The pregnancy will be reported as an AE.

### 10.6.9 Review Inclusion/Exclusion Criteria

At Visit 1, inclusion/exclusion criteria will be reviewed to ensure patients' eligibility for participation in the study.

### 10.6.10 Collect and Review Patient Diary

At Visits 2 and 3, patient diaries will be collected and reviewed for compliance with the protocol.

### 10.6.11 Provide Patient Diary

Patients will be given a diary with instructions on dosage administration and diary completion. The diary will be reviewed by the study staff at Visits 2 and 3 (when applicable).

### 10.6.12 Dispense Study Product

After the Investigator has determined that the study participant meets the inclusion/exclusion criteria for the study the "Independent Dispenser" will dispense one 60 gram tube of study product to the patient using the lowest patient randomization number available at that investigative site, and if necessary, at Visit 2 (re-dispense the same tube to the patient, i.e., no new tube will be provided) with dosing instructions. The Independent Dispenser will ensure the study product logs are reported correctly. Eligible household members and close contacts of the patient will be administered generic Permethrin cream and will follow the appropriate application and decontamination instructions.

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### 10.6.13 Collect and Weigh Study Product

Study product tubes will be collected and weighed at Visit 2 or Visit 3 (in cases when re-treatment is required or if the patient inadvertently did not return the study product at Visit 2) by the Independent Dispenser and checked for compliance or evidence of tampering with the blind. The weight will be recorded in the drug accountability log.

## 10.7 Adverse Events

The patients will be monitored throughout the study for any AEs. Adverse events will be collected through both solicited and unsolicited means and subsequently coded in tabular form using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 20.0 or higher) AE Dictionary. The patients will be encouraged to report signs, symptoms, and any changes in health to the clinic staff. Severity of each AE will be determined by the staff based on observation and questioning of the patients. The Investigator will judge the relationship of the event to the study treatments. AEs should be followed up until they have resolved or stabilized.

### 10.7.1 Adverse Event Definitions

Adverse Event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease, temporally associated with the use of a medicinal (investigational) product, whether or not related to this product. This includes events not seen at baseline, or worsened even if present at baseline.

Unexpected Adverse Event: An AE where the nature or severity of is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Adverse Drug Reaction: All noxious and unintended responses to a medical product related to any dose should be considered adverse drug reactions. The response to a 'medical product' means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

### 10.7.2 Severity of Adverse Event

The severity of the AE will be graded by the Investigator using the following criteria as guidelines:

- MILD: Awareness of symptom but does not interfere with routine activities.
- MODERATE: Discomfort sufficient to interfere with routine activities.
- SEVERE: Impossible to perform routine activities.

### 10.7.3 Relationship of Adverse Event

Relationship to the study product will be evaluated by the Investigator as follows:

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- Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility
- Related: A causal relationship between the study treatment and the AE is a reasonable possibility.

### 10.8 Serious Adverse Events

#### 10.8.1 Definition of a Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose suggests a medically significant hazard, including any event that:

- Results in death: includes all deaths, even those that appear to be completely unrelated to study treatment (e.g., car accident where patient is a passenger).
- Is life-threatening: in the view of the Investigator, the patient is at immediate risk of death at the time of the event.
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Causes congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the serious outcomes listed above (e.g., intensive treatment in an emergency room, convulsions that do not result in hospitalizations). Emergency Room visits that require medical or surgical intervention to prevent one of the other serious outcomes listed above are considered an SAE.

#### 10.8.2 Reporting Serious Adverse Events

##### Investigator Reporting of SAEs

Adverse events that meet the above criteria for "Serious" will be reported to the Sponsor and IRB within 24 hours of notice whether or not they are considered expected or drug-related. All SAEs will be reported as per applicable regulations. All SAEs encountered during the study will be reported on the appropriate form and summarized in the final report.

**Any serious or unexpected AEs should be reported to Novum within 24 hours. Following is the contact information:**

Gail Gongas  
Vice President, Clinical Trials and Data Management  
Cell Phone 412-606-1603  
Phone: 412-363-3300 x 522  
Fax: 412-291-3171

Or

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Paolo Fanzio, MD  
Medical Director  
Phone: 412-363-3300 x 597  
Fax: 412-291-3171

### Novum will report any SAE to Sponsor:

Documentation of serious or unexpected AEs and follow-up information should be sent to the Sponsor within 24 hours from Novum being made aware of the SAE. Following is the contact information:

Pratik Kamini  
GM- Strategy & Commercial  
Encube Ethicals Pvt Ltd  
Phone: +91-22-6228-8000 Ext 8003  
Mobile: +91-98-2047-9316  
Email: Pratik.K@EncubeEthicals.com

Novum will be responsible for notifying the FDA of any SAEs. Novum must notify FDA of fatal or life-threatening SAE as soon as possible, but no later than seven calendar days from reporting the event by the Investigator.

Novum will inform all the participating investigators of any SAEs reported at other study sites within 15 days from the initial report. Sites outside of the US will be responsible for reporting to their local regulatory authorities as appropriate.

## 11.0 STATISTICAL METHODS

### 11.1 Statistical Plan

A Statistical Analysis Plan (SAP), detailing the intended statistical analyses of the study data, will be prepared as a separate document and finalized before database lock. Any deviation from the original SAP will be described and justified in the final report, as appropriate. The procedure for accounting for missing, unused and spurious data will be included in the SAP.

All statistical analyses will be performed by Novum Pharmaceutical Research Services and conducted using the Statistical Analysis System (SAS®), Version 9.4 or higher. Datasets will be prepared using headings from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) implementation for human clinical trials and Analysis Dataset Model (ADaM).

### 11.2 Determination of Sample Size

For the primary endpoint analysis (proportion of patients in the PP population who are considered to be a Therapeutic Cure on Day 28 ± 4), sample size is estimated for therapeutic equivalence of the Test to the Reference product.

Based on data from a previous bioequivalence study conducted to support approval of the first generic product of permethrin cream, 5%, the therapeutic cure rate ( $p_R$ ) of the Reference product (Elimate™ permethrin cream 5%) is expected to be about 88% in the PP population. Assuming that the Therapeutic Cure rate for the Test group ( $p_T$ ) is an absolute difference of 5% lower than the Reference

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group (i.e.,  $p_T - p_R = -5\%$ ), a sample size of 107 patients in each active group in PP population will provide at least 90% power to demonstrate therapeutic equivalence (i.e., the 90% confidence interval [Yates' continuity corrected] on  $p_T - p_R$  is within a defined equivalence range [-20%, +20%]).

To allow for approximately 14% of patients who may drop out from the study or are otherwise non-evaluable, approximately 250 patients (125 in each treatment group) will be randomized, such that there will be an estimated 214 patients (107 per group) in the PP population for statistical evaluation of therapeutic equivalence.

### 11.3 Study Populations

#### 11.3.1 Per-Protocol Population

The PP population will include:

- Met the inclusion/exclusion criteria as defined in this protocol at Visit 1.
- Did not take any prohibited medications throughout the study.
- Did not have any significant deviations from the protocol.
- Did not develop any concurrent dermatological condition or illness exhibiting symptoms similar to scabies, or symptoms that in the Investigator's opinion would interfere with endpoint assessments.
- Completed the last study visit (Visit 3) Day  $28 \pm 4$ .

Patients will be included in the PP population as treatment failures in the final analysis on Day 28 (provided they had no significant protocol deviations) if they 1) withdrew from the study because of lack of efficacy, 2) show therapeutic cure at Day  $14 \pm 4$  but re-infestation at Day  $28 \pm 4$ , or 3) do not respond to the initial treatment and have new lesions or microscopic confirmation of mites, ova, or fecal matter on Day  $14 \pm 4$ .

#### 11.3.2 Safety Population

The safety population will include all patients who are randomized who applied at least one dose of the assigned study product.

### 11.4 Baseline Comparability

Baseline comparability of all treatment groups will be evaluated separately in the PP and Safety populations. The following baseline demographics (determined from their initial study visit) will be evaluated:

- Age (years)
- Gender (male/female)
- Ethnicity (Hispanic/non-Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native, Other)

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- Baseline severity score of nocturnal itching
- Severity of lesion count infestation pretreatment (mild, moderate, severe)

Summary tables by treatment group will be presented. Continuous variables will be summarized using descriptive statistics (number of observations, median, minimum, maximum, mean and standard deviation). Categorical variables will be summarized using frequencies and percentage. Baseline treatment comparisons will be presented using Chi-Square or Cochran-Mantel-Haenszel (CMH) tests for the categorical variables, and Analysis of Variance (ANOVA) for the continuous variables.

All data will be listed by treatment and patient.

### 11.5 Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients in each treatment group with Therapeutic Cure (parasitological cure plus clinical cure) of scabies at the test-of-cure visit conducted at Day 28 ± 4. A parasitological cure is defined as failure to demonstrate microscopically the presence of scabies infestation (i.e., no living mites, no viable mite eggs, and no mite fecal matter present). A clinical cure is defined as visual evidence of absence of new lesions and healing of original lesions, regardless the presence of post-scabietic nodules (i.e., post-scabietic nodules need not be considered as new lesions or persistence of old lesions).

Patients who do not respond to the initial treatment and have new lesions or microscopic confirmation of mites, ova, or fecal matter on Day 14 ± 4 will be treated as treatment failure in the final analysis on Day 28.

### 11.6 Efficacy Analyses

#### Primary Analysis:

Therapeutic equivalence of the Test product to the Reference product based on the primary endpoint will be evaluated in the PP population. If the 90% confidence interval on the absolute difference between the proportion of patients who are considered a Therapeutic Cure (primary) in the Test and Reference groups is contained within the range [-20%, +20%] then therapeutic equivalence of the Test product to the Reference product will be considered to have been demonstrated.

#### Supportive Analyses:

The following supportive analyses will be performed for the primary endpoint:

1. The primary analysis will be performed including patients who completed Visit 2 within 14 ± 2 days and Visit 3 within 28 ± 4 days.
2. The primary analysis will be performed including patients who completed Visit 2 within 14 ± 2 days and Visit 3 between Day 26 and Day 32, inclusive.
3. The primary analysis will be performed including patients who completed Visit 2 within 14 ± 2 days and Visit 3 within 28 ± 2 days.

To declare therapeutic equivalence of the Test product to the Reference product, therapeutic equivalence must be demonstrated for only the primary analysis.

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### 11.7 Treatment-by-Site Interaction and Pooling of Clinical Sites

As this is a multiple-site study, the interaction of treatment-by-site may be evaluated for the primary efficacy endpoint in the PP population (for equivalence testing). The treatment-by-site interaction will be evaluated by the Breslow-Day test for homogeneity of the odds ratio at the 5% significance level ( $p < 0.05$ ). A site(s) with a low enrollment rate(s) may be pooled with its geographically closest site, so as to avoid bias in the estimation of a treatment-by-site interaction effect. The pooling will be done for low enrolling sites that account for less than 4-7% of the total number of patients in the PP population at the site with the highest enrolling rate in the PP population. If the treatment-by-site interaction term is found to be statistically significant ( $p < 0.05$ ) for the primary endpoint, then the interaction term will also be assessed for clinical relevance before pooling the data across sites. This will include examination of Therapeutic Cure rates at each site where sample sizes per treatment may be influential in the assessment of the interaction.

### 11.8 Safety Analysis

Adverse events will be classified using standard MedDRA terminology Version 20.0 or higher and summarized by treatment group. Summary tables comparing the type, incidence, date of onset, date of resolution, severity, action taken, outcome and Investigator's opinion of relationship to the study product will be prepared by treatment group. If sufficient data exist, AE frequencies will be compared between treatments using Fisher's exact test or a similar test in the Safety population.

Signs and symptoms of scabies will not be considered AEs, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers that it is in the patient's best interest to be dropped from continued participation in the study and given alternative therapy for their condition.

Concomitant medication use during the study will be tabulated by patient.

## 12.0 REGULATORY OBLIGATIONS

### 12.1 Institutional Review Board

The study protocol, ICF, Investigator's Brochure, or package insert (as applicable), and any specific advertising will be submitted to, and approved by, an IRB before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification of the board's approval along with a description by profession and gender of the board's composition will be provided to the Sponsor.

### 12.2 Study Documentation

This study will be conducted in compliance with the protocol; GCP and all applicable regulations, including the Federal Food, Drug and Cosmetics Act, US applicable Code of Federal Regulations (title 21), parts 50, 56, 312, 320, and any IRB requirements relative to clinical studies; and the Declaration of Helsinki, June 1964, as modified by the 64<sup>th</sup> World Medical Association General Assembly, October 2013.<sup>16-19</sup> The Investigator will permit trial-related monitoring, audits, IRB review and regulatory inspections providing direct access to source data/documents.

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### 12.2.1 Protocol

The Investigator indicated on FDA Form 1572 will act as the Principal Investigator at each study site. Protocols will be noted as approved by placement of the Novum Representative's signature on the cover page. The Sponsor of the study will also approve the protocol by having a study-responsible individual sign the protocol cover page. The Principal Investigator will sign the protocol signature page indicating their agreement to conduct the study according to the protocol.

### 12.2.2 Informed Consent

An ICF that includes all of the relevant elements currently required by FDA, ICH, and local state regulations will be provided to each prospective study patient before enrollment into the study. The type and method of study, tests to be administered, any potential or possible hazards, and the patient's right to withdraw from the study at any time will be explained to the patients by the Investigator or designee. Once the Investigator or designee is assured that an individual candidate understands the implications of participating in this study, the patient will be asked to give consent by signing and dating in the appropriate areas of the ICF. The Investigator or designee will also sign and date the form, along with a staff member who will sign the ICF as a witness to verify that the patient has indeed received information. If any other language is required, translation will be performed by a certified translator. A copy of the ICF will be provided to the patient. For patients who are considered minors in the state the study is being conducted (< 18 years in most states) the parent or legal guardian should sign the consent form and the child will be required to sign a patient "assent" form, as appropriate. Patients 11-17 years of age will read and sign an IRB-approved assent form and patients 6-10 years of age will provide verbal assent. Patients 2-5 years of age will be exempt from providing assent based on the child's comprehension and cognitive skills.

### 12.2.3 Protocol and Informed Consent Changes

Sponsor approved changes to the protocol or the ICF will be implemented as revisions to the original documents and will require additional review and approval by the IRB. Revisions to the original protocol will be documented in amendments, incorporated as a preface to the new version. Any revision that substantially alters the study design or increases potential risk to the patient requires the patient's consent to continue in the study. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and ICF amendments/revisions, along with letters noting IRB approval, will be submitted to the Sponsor.

### 12.2.4 Source Documents and Electronic Case Report Forms (eCRF)

All patients will be identified by initials, date of birth and a unique patient number. Source documents will be used to record all study-related data. Source document entries will be used to complete eCRFs. A set of eCRFs will be completed for each patient randomized in the study. All data and eCRFs will be reviewed, evaluated and signed by the Investigator.

The original source documents and a copy of the corresponding eCRFs will be retained by the Investigator. Patients who terminate early from the study will have the Visit 3 (End of Study) source/eCRF completed.

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### 12.2.5 Drug Accountability

All study product receipt, inventory, dispensing, dosing and reconciliation records will be maintained in compliance with federal regulations. The study product will be dispensed to qualified study patients according to established procedures. At the end of the study (after the database has been locked) all used and unused study product will be returned to Sponsor or designee.

### 12.2.6 Drug Storage

Study product will be stored at controlled room temperature 20-25°C (68-77°F) [USP Controlled Room Temperature] in a secure place with access by authorized individuals only. The Investigator will be responsible for maintaining accurate records of drug receipt, dispensing, and return. After finalizing the study report, all partially used and unused study product will be returned to Sponsor or designee.

### 12.2.7 Retention of Reserve Samples

For every study product shipment received at the Investigator site, the Investigator (or designee) will randomly select at least one block of study product for retention, unless otherwise instructed by the Sponsor and/or Novum. These retention samples should be stored under the appropriate storage conditions for a minimum of 5 years following the application approval or, if not approved, at least 5 years after the completion of the study. Retention samples should not be returned to Sponsor/CRO/packaging group at any time.

### 12.2.8 Pregnancies

Patients with a positive pregnancy test during screening will not be enrolled in the study. Patients who report that they have become pregnant during the study or have a positive pregnancy test at Visit 3 will be followed to completion of the pregnancy. The pregnancy will be reported as an AE.

Female patients of childbearing potential must have been using and must agree to continue to use accepted methods of birth control, throughout the study. Acceptable methods of birth control include total abstinence, intrauterine device, a double-barrier method (such as condom with spermicide or diaphragm with spermicide), oral, transdermal, injected, or implanted non-hormonal or hormonal contraceptive throughout the study. Female patients using hormonal contraceptives should have been on the same product/dosing regimen for at least 28 days before Visit 1 and should not change this regimen during the study. A sterile sexual partner is not considered an adequate form of birth control. Before study enrollment women of childbearing potential must be advised of the importance of avoiding pregnancy during study participation.

A negative result of a urine pregnancy test having a minimum sensitivity of at least 50 mIU/mL for human chorionic gonadotropin (hCG) should be obtained, before study participation. Pregnancy testing will be performed at Visits 1 and 3 and the results of all pregnancy tests (positive or negative) will be documented.

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If following initiation of study treatment, it is subsequently discovered that a study patient is pregnant or may have been pregnant at the time of study product exposure, the study product will be permanently discontinued. The Principal Investigator or designee must immediately notify the Medical Monitor of this event. Reporting timelines and Novum/Sponsor contact will be consistent with SAE reporting guidelines (i.e., pregnancies will be reported to the Sponsor/Novum within 24 hours to the contacts listed in section 10.8.2).

Protocol-required procedures for study discontinuation and follow-up must be performed on the patient. Other appropriate pregnancy follow-up procedures should be considered if indicated. All follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome will be communicated as per the above guidelines. Infants should be followed for a minimum of eight weeks after birth.

### **12.2.9 Reporting Safety Information to the IRB**

The Investigator must promptly report to the Investigator's IRB all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs occurring during the study, regardless of the assessed causality.<sup>20</sup>

### **12.2.10 Record Retention**

All drug accountability records, eCRFs, source data and related regulatory documents must be retained for at least two years following completion of the study or Test product approval for marketing by the FDA.

### **12.2.11 Study Monitoring and Auditing**

Novum will be responsible for monitoring the study according to GCP and applicable regulations. Monitoring visits are for the purpose of confirming adherence to the protocol and to verify complete and accurate data collection. The clinical site will make all records associated with the study available to Novum's representative during such visits and audits.

The study may be subject to audit by the Sponsor, Sponsor Representative or by regulatory authorities. If such an audit occurs the Investigator must agree to allow access to required patient records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of study procedures.

### **12.2.12 End of the Trial**

The end of the trial is defined as the time at which the last patient has completed their last visit in the study. Upon completion of the study, the study product will no longer be available to the patient but the Investigator can, at their discretion, discuss alternative treatments with the patient.

### **12.2.13 Clinical Study Report**

At the end of the study a full report per requirements of Sponsor and regulatory authorities will be prepared which will include a narrative of the clinical conduct and results of the study, a statistical report including a description of the analysis performed, and other documentation as

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may be appropriate. The report will be in electronic format according to eCTD and ICH formatting standards and guidelines.<sup>21</sup>

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A Randomized, Double-Blind, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Permethrin Cream, 5% (Encube Ethicals) Compared to Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc.) in the Treatment of Scabies

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### **14.0 APPENDICES**

#### **14.1 APPENDIX A: RATING OF SCABIES SIGNS AND SYMPTOMS**

##### PRURITUS

At each clinic visit, patients will be asked to rate the severity of pruritus (overall itch intensity and effect of itching on nighttime sleep) on the following 4-point scale.

0 = none (complete absence of itching)

1 = mild (slight itching, no sleep loss)

2 = moderate (definitely present, interrupts sleep)

3 = severe (marked, intense, cannot sleep)

##### LESION COUNT

At each clinic visit, the lesion count will be evaluated and rated as follows:

< 50 = mild

50-100 = moderate

> 100 = severe

## **CONFIDENTIAL PROTOCOL**

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### **14.2 APPENDIX B: DERMOSCOPY AND MICROSCOPY FOR SCABIES DIAGNOSIS**

#### **SKIN SCRAPING/MICROSCOPY**

Skin scrapings will be obtained with a sterile scalpel after the application of 1 drop of mineral oil onto the lesion. The scraped material will be transferred to a slide and covered with a cover slip. Reading is to be performed immediately under a microscope, or within 3 hours, at 40 X magnification. The number of scraped sites until the examination is declared negative will be left to the recognition of the attending Investigator in relation to the clinical picture.

A single scraping is not considered sufficient to adequately define parasitological cure.

The best efforts should be made to attempt valid skin scrapings for microscopic examinations, even in case of virtually healed lesions as appropriate.

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**14.3 APPENDIX C: PRODUCT INSERT FOR ELIMITE™**

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**14.4 APPENDIX D: AMENDMENTS TO THE PROTOCOL**

Amendment	Date
1	10/31/2017

The following revisions were made to the protocol dated 05/02/2017.

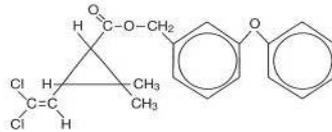
- Removed Yates’ correction in the primary analysis.
- Removed the secondary endpoint and related analysis language.
- Added supportive analyses.
- Revised the PP population and Safety population inclusion criteria.
- Added justification for the change in statistics and deviation from the FDA guidance.
- Made minor typographical corrections throughout the document.



**ELIMITE™ CREAM**  
\*W/W  
Rx Only  
(PERMETHRIN) 5%\*

**DESCRIPTION**

ELIMITE™ (permethrin) 5% Cream is a topical scabicide agent for the treatment of infestation with *Sarcoptes scabiei* (scabies). It is available in an off-white, vanishing cream base. ELIMITE™ (permethrin) 5% Cream is for topical use only.



**Chemical Name** - The permethrin used is an approximate 1:3 mixture of the cis and trans isomers of the pyrethroid 3-(2,2-dichloroethyl)-2,2-dimethylcyclopropanecarboxylic acid, (3-phenoxyphenyl) methyl ester. Permethrin has a molecular formula of  $C_{21}H_{29}Cl_2O_3$  and a molecular weight of 391.29. It is a yellow to light orange-brown, low melting solid or viscous liquid.

**Active Ingredient** - Each gram contains permethrin 50 mg (5%).

**Inactive Ingredients** - Butylated hydroxytoluene, carbomer homopolymer type B, fractionated coconut oil, glycerin, glyceryl monostearate, isopropyl myristate, lanolin alcohols, mineral oil, polyoxyethylene cetyl ethers, purified water, and sodium hydroxide. Formaldehyde 1 mg (0.1%) is added as a preservative.

**CLINICAL PHARMACOLOGY**

Permethrin, a pyrethroid, is active against a broad range of pests including lice, ticks, fleas, mites, and other arthropods. It acts on the nerve cell membrane to disrupt the sodium channel current by which the polarization of the membrane is regulated. Delayed repolarization and paralysis of the pests are the consequences of this disturbance.

Permethrin is rapidly metabolized by ester hydrolysis to inactive metabolites which are excreted primarily in the urine. Although the amount of permethrin absorbed after a single application of the 5% cream has not been determined precisely, data from studies with  $^{14}C$ -labeled permethrin and absorption studies of the cream applied to patients with moderate to severe scabies indicate it is 2% or less of the amount applied.

**INDICATIONS AND USAGE**

ELIMITE™ (permethrin) 5% Cream is indicated for the treatment of infestation with *Sarcoptes scabiei* (scabies).

**CONTRAINDICATIONS**

ELIMITE™ (permethrin) 5% Cream is contraindicated in patients with known hypersensitivity to any of its components, to any synthetic pyrethroid or pyrethrin.

**WARNINGS**

If hypersensitivity to ELIMITE™ (permethrin) 5% Cream occurs, discontinue use.

**PRECAUTIONS**

**General** - Scabies infestation is often accompanied by pruritus, edema, and erythema. Treatment with ELIMITE™ (permethrin) 5% Cream may temporarily exacerbate these conditions.

**Information for Patients** - Patients with scabies should be advised that itching, mild burning and/or stinging may occur after application of ELIMITE™ (permethrin) 5% Cream. In clinical trials, approximately 75% of patients treated with ELIMITE™ (permethrin) 5% Cream who continued to manifest pruritus at 2 weeks had cessation by 4 weeks. If irritation persists, they should consult their physician. ELIMITE™ (permethrin) 5% Cream may be very mildly irritating to the eyes. Patients should be advised to avoid contact with eyes during application and to flush with water immediately if ELIMITE™ (permethrin) 5% Cream gets in the eyes.

**Carcinogenesis, Mutagenesis, Impairment of Fertility** - Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice when permethrin was given in their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of *in vitro* and *in vivo* genetic toxicity studies.

Permethrin did not have any adverse effect on reproductive function at a dose of 180 mg/kg/day orally in a three-generation rat study.

**Pregnancy: Teratogenic Effects: Pregnancy Category B** - Reproduction studies have been performed in mice, rats, and rabbits (200 to 400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Nursing Mothers** - It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

**Pediatric Use** - ELIMITE™ (permethrin) 5% Cream is safe and effective in pediatric patients two months of age and older. Safety and effectiveness in infants less than two months of age have not been established.

**Geriatric Use** - Clinical studies of ELIMITE™ (permethrin) 5% Cream did not identify sufficient numbers of subjects aged 65 and over to allow a definitive statement regarding whether elderly subjects respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. This drug is known to be substantially excreted by the kidney. However, since topical permethrin is metabolized in the liver and excreted in the urine as inactive metabolites, there does not appear to be an increased risk of toxic reactions in patients with impaired renal function when used as labeled.

#### ADVERSE REACTIONS

In clinical trials, generally mild and transient burning and stinging followed application with ELIMITE™ (permethrin) 5% Cream in 10% of patients and was associated with the severity of infestation. Pruritus was reported in 7% of patients at various times post-application. Erythema, numbness, tingling, and rash were reported in 1 to 2% or less of patients (see **PRECAUTIONS-General**). Other adverse events reported since marketing ELIMITE™ (permethrin) 5% Cream include: headache, fever, dizziness, abdominal pain, diarrhea and nausea and/or vomiting. Although extremely uncommon and not expected when used as directed (see **DOSAGE AND ADMINISTRATION**), rare occurrences of seizure have been reported. None have been medically confirmed as associated with ELIMITE™ treatment.

#### OVERDOSAGE

No instance of accidental ingestion of ELIMITE™ (permethrin) 5% Cream has been reported. If ingested, gastric lavage and general supportive measures should be employed. Excessive topical use (see **DOSAGE AND ADMINISTRATION**) may result in increased irritation and erythema.

#### DOSAGE AND ADMINISTRATION

**Adults and children** -Thoroughly massage ELIMITE™ (permethrin) 5% Cream into the skin from the head to the soles of the feet. Scabies rarely infests the scalp of adults, although the hairline, neck, temple, and forehead may be infested in infants and geriatric patients. Usually 30 grams is sufficient for an average adult. The cream should be removed by washing (shower or bath) after 8 to 14 hours. Infants should be treated on the scalp, temple, and forehead. **ONE APPLICATION IS GENERALLY CURATIVE.**

Patients may experience persistent pruritus after treatment. This is rarely a sign of treatment failure and is not an indication for retreatment. Demonstrable living mites after 14 days indicate that retreatment is necessary.

#### HOW SUPPLIED

ELIMITE™ 5% Cream is available as follows:  
60 g tube (NDC 40076-230-60)

#### STORAGE

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].



Manufactured for Prestium Pharma, Inc.  
Newtown, PA 18940

Manufactured by DPT Laboratories, Ltd.,  
San Antonio, TX 78215

Rev. 08/15