

Drug Class Update with New Drug Evaluation: Topical Antiparasitics

Date of Review: October 2021

Generic Name: abametapir

Current Status of PDL Class:
See **Appendix 1.**

Purpose for Class Update:

To evaluate the available comparative evidence for topical antiparasitic agents and assess need to change policy since last class update. To evaluate the place in therapy for abametapir, a topical metalloproteinase inhibitor Food and Drug Administration (FDA)-approved to treat head louse infestations in patients 6 months of age and older with a single application.

Research Questions:

1. What is the comparative efficacy or effectiveness of topical antiparasitic agents for use in head louse infestation and scabies?
2. What is the comparative safety of topical antiparasitic agents?
3. Is abametapir safer or more effective than any currently available therapies for head louse infestations?
4. Are there any subgroups (based on age, gender, pregnancy status, ethnicity, comorbidities, or housing status) that would benefit or be harmed from topical antiparasitic medications?

Conclusions:

- Since the previous review additional evidence has become available with 1 new high quality comparative systematic review. There is 1 new agent, 1 indication expansion, and a prescription to over the counter (OTC) status switch.
- A Cochrane review^{1,2} focused on comparative scabies therapy, primarily in developing countries.
 - Low-certainty evidence shows permethrin 5% cream may have a higher clearance after 1 week compared to standard dose (200 mcg/kg) oral ivermectin (65% vs. 43%, relative risk [RR] 0.65, 95% confidence interval [CI] 0.54 to 0.78) and little to no difference by week 2 (74% vs. 68%; RR 0.91, 95% CI 0.76 to 1.08).
 - Moderate-certainty evidence shows that with 1 to 3 doses/applications of either oral ivermectin or permethrin, there may be little to no difference in complete clearance at 4 weeks (93% permethrin vs. 86% ivermectin; RR 0.92, 95% CI 0.82 to 1.03), and comparing a single treatment of each shows little to no difference in complete cure at 1 week (73% vs. 68%; RR 0.93, 95% CI 0.74 to 1.17).

Date of Last Review: March 2016

Dates of Literature Search: 12/01/1015 - 07/06/2021

Brand Name (Manufacturer): Xeglyze (Dr. Reddy's Laboratories)

Dossier Received: no

- Moderate-certainty evidence shows little to no difference in complete clearance rates after 4 weeks of treatment of oral ivermectin compared to topical ivermectin (97% vs. 96%; RR 0.99, 95% CI 0.95 to 1.03) or permethrin compared to topical ivermectin (94% vs. 96%; RR 1.02, 95% CI 0.96 to 1.08).
- High-certainty evidence shows little to no difference in cure rate between different ivermectin doses (90% 2 doses vs. 87% 1 doses; RR 0.97, 95% CI 0.83 to 1.14).
- There was suboptimal reporting of adverse events in studies. There is low-certainty evidence of no difference of patients experiencing at least one adverse drug reaction by 4 weeks between oral ivermectin, topical ivermectin, and topical permethrin.
- Abametapir was approved for treatment of head lice based on the efficacy of two identical, poor-quality, double-blind, vehicle-controlled (VC) trials in patients 6 months and older with active louse infections and no previous treatment.^{3,4} Quality rating is due to overall high risk of bias in both trials.
- There is low-quality evidence that a single application of abametapir 0.74% is statistically superior to VC for proportion of patients louse-free at all study follow up visits (days 1, 7, 14) for both study 1 (81.1% vs. 50.9%; odds ratio [OR] 4.01; 95% CI 1.70 to 9.48; p=0.001, absolute risk reduction [ARR] 30.2% number needed to treat [NNT] 4) and study 2 (81.8% vs. 41.2%; OR 5.50; 95% CI 2.20 to 13.73; p<0.001; ARR 34.6%; NNT 3).³
- Erythema (4%), rash (3.2%), and skin burning sensation (2.6%) were the most frequently reported treatment emergent adverse events (TEAE). There was one serious adverse event not judged to be due to the study medication. No TEAE resulted in death or study withdrawal.³
- There is low-quality evidence that abametapir is safe compared to placebo for single application in the study population. Long-term data are lacking, safety data are insufficient in patients who are pregnant, lactating, less than 6 months old, over 65 years old, non-white and non-Hispanic, and patients with underlying skin conditions.³
- Product contains benzyl alcohol and should not be used in those less than 6 months old.⁴

Recommendations:

- Maintain abametapir as non-preferred on the Oregon Health Plan (OHP) preferred drug list (PDL).
- Move ivermectin cream (SOOLANTRA), indicated for rosacea, to the topical antiparasitic class and designate as non-preferred.
- Recent evidence does not support additional clinical changes to the PDL.
- After executive session, VanaLice® gel was made non-preferred.

Summary of Prior Reviews and Current Policy

- The 2016 class update found no evidence to dispute permethrin as first-line therapy.
- Permethrin formulations and piperonyl butoxide formulations are preferred on the PDL (see **Appendix 1** for a list of drugs in the topical antiparasitic PDL class).
- There are no class or product specific prior authorization criteria for the topical antiparasitic agents.

The treatment of lice and scabies are both funded on the Oregon List of Prioritized Health Services, while rosacea is an unfunded condition.⁵ There were just over 100 patient requests for agents in this class in first quarter of 2021, and the majority of utilization was for preferred agents.

Background:

Topical antiparasitic agents can be used in variety of dermatological disorders. Most common indications are for lice, scabies, and rosacea.

Louse Infestations

Louse infestations manifest as pediculosis capitis (head), pediculosis corporis (body), and pediculosis pubis/pediculosis ciliaris (pubic area, eyelashes) and are the result of three related varieties a single lice species.⁶⁻⁸ Transmission varies by type. Head louse infestations generally result from direct contact with the head of infected individuals and are not a sign of poor hygiene; body louse infestations are a significant problem in settings of poverty, crowding, and low personal hygiene; while pubic louse infestations primarily spread via sexual contact.⁶⁻⁸ Research on topical antiparasitic use for louse infestations generally focuses on head louse.

Head lice have a life span of about one month. Eggs are glued (“cemented”) onto the base of the hair. Nymphs hatch 8 days later and mature in 8 days. Adult lice feed on host blood and can survive just over 2 days without a host.⁶ Diagnosis of a head louse infestation requires finding a living louse on an individual’s scalp hair. Unhatched eggs can indicate a live or past infection and are difficult to differentiate from an empty eggshell without a microscope. Both unhatched eggs and empty eggshells may be referred to as “nits” in the literature.^{6,9,10} Presence of nits alone is not adequate for diagnosis of an active infestation and its use results in significant overdiagnosis, false presumption of failed treatment, and unnecessary retreatment. Presence of nits are not predictive of future louse infestation.⁹ Studies have found that roughly 2/3 of patients with nits do not have active infections.⁹ Use of a fine-tooth comb improves speed and accuracy of diagnosis of active infections while direct observation without combing often underestimates active infestation. Wet combing is more effective for diagnosis than visual inspection without combing (91% vs 29% sensitivity) but has not been directly compared to dry combing.⁶ Combing may not be feasible with all hair types and diagnosis in curly/frizzy hair is more difficult regardless of method.⁹

Head louse infestations are often asymptomatic, though affected individuals may have symptoms such as itching which may impact sleep or concentration. Scratching can result in secondary skin infections and lymphadenopathies.⁹ Infestations primarily affect children ages 4 to 13 years in childcare and elementary school, and their household contacts. Girls are 2-10 fold more likely to be infested than boys.⁹ There is a lower incidence in Black children, likely due to lice being unable to grasp certain hair shapes and widths.⁶

Topical pediculides such as pyrethroids (pyrethrins, permethrin), malathion, benzyl alcohol, spinosad, and topical ivermectin are often used to treat lice infestations. Pyrethroids are preferred first-line options in locations without documented resistance.^{6,10,11} Lindane is not recommended first-line as it is associated with rare, severe neurological toxicity (seizures, death) and widespread resistance.⁶ Repeat administration 7 to 9 days after initial treatment is recommended (except topical ivermectin and lindane) as they do not kill unhatched eggs. This second treatment does not indicate treatment failure. Resistance to pyrethrins, pyrethroid insecticides, organophosphate, and carbamate insecticides have been documented and vary by location.^{9,12-14} Resistance to pyrethroid-based pediculicides is associated with the knockdown resistance (*kdr*) trait, which is thought to result from the homozygous and heterozygous presence of several different mutant alleles, including M815I, T917I, and L920F.^{12,14} These mutations affect the voltage-gated sodium channel α -subunit gene, seem to be increasing over time, and generally correspond to simultaneously reduced effectiveness of permethrin in various studies.^{13,15} Studies involving lice with these specific gene mutations have shown reduced *ex vivo* effectiveness of permethrin, though an observational study did not show treatment failure and high-quality, prospective *in vivo* studies on the correlation of *kdr* mutations and treatment failure are lacking.^{12,13,16,17} Local resistance patterns in specific states is difficult to obtain.^{6,10} One study, including 4 Oregon samples from the Portland metro area and 2 samples from the Vancouver, WA area found a resistance allele frequency of 100% in 5 of 6 samples and 50% to <100% from the remaining sample.¹⁵ Oral ivermectin can be considered in refractory infestation, though not in pregnant women or in children weighing less than 15 kg due to lack of safety data.⁶ Wet combing with specific lice combs can be attempted to mechanically remove lice in those too young or wishing to avoid medication treatment. This method is labor intensive and effectiveness has varied across studies.⁶ New treatment

candidates should be tested against an effective pediculide or other head louse treatment used in the same country on individuals with a substantial number of living lice.⁹ An efficacy of 85% is desired for new products to the market.⁹

Environmental cleaning methods are often adequate to control pediculosis corporis infestations.⁷ Use of topical pediculicides (permethrin or topical pyrethrins with piperonyl butoxide) with manual nit removal are generally the preferred treatments for pediculosis pubis.⁸ A second application of topical pediculicides is usually necessary.⁸

Scabies

Scabies is a skin infestation caused by the *Sarcoptes scabiei* var. *hominis* mite which burrows into the skin.^{18,19} It has a life cycle of 10-14 days, though patients with classic disease are generally symptom free during a 1-2 month incubation, and up to several months in the elderly.²⁰ Classic, non-crusted scabies presents as an intensely pruritic, usually nocturnal, itch and can result in disseminated, excoriated, erythematous papules typically on the anterior trunk, limbs, wrists, finger webbing, axillae, areolae, and genitalia.^{18,19} Crusted scabies (synonymous with hyperkeratotic scabies, formerly called “Norwegian scabies”) is associated with immunocompromised individuals and typically has a high mite burden.^{18,20} The incubation period for crusted scabies may be only 4-5 days due to a larger infestation upon acquisition.²⁰ Pruritus may be absent in crusted scabies, but those infested manifest thick scales, crusts, and fissures.^{18,19} The scalp, hands, and feet are often involved.¹⁸ Both types can result in secondary bacterial infections, typically streptococcal or staphylococcal in origin, and poststreptococcal glomerulonephritis and other complications can occur.¹⁸

Transmission for both types generally occurs during skin-to-skin contact among family members and between sexual partners. Fomite transmission is rare with classic scabies but may occur with crusted scabies.^{18,20} Crowded conditions increase risk of infestations. Scabies is more common in resource limited regions, however, outbreaks can occur high-income countries in institutionalized settings such as long-term care facilities and prisons.^{18,21} Houseless individuals and displaced groups, such those affected by natural disasters, are at higher risk.²¹

Diagnosis is often clinically made based upon appearance and distribution of rash and the presence of burrows. Formalized 2018 diagnostic criteria from the International Alliance for the Control of Scabies are also sometimes used.²¹ Diagnosis is confirmed using microscopy and dermoscopy, however these have low sensitivity in finding mites, eggs, or feces. Using microscopy, mite detection rates can range from 10 to 70%, making it necessary to test eruptions in multiple areas of the body in classic scabies, and negative results do not exclude the diagnosis.^{18,20} Dermoscopy has lower specificity than microscopy and is more difficult in highly pigmented skin.¹⁸ Eosinophilia or increased immunoglobulin (Ig) E can be present in cases of scabies, but presence or absence does not confirm or rule out diagnosis.^{18,20}

Treatment varies by country. In the United States, topical permethrin is the preferred first-line agent and oral ivermectin (2 doses) is considered an alternative first-line option for certain populations. Treatments with malathion, topical ivermectin, crotamiton, spinosad, or topical sulfur are alternatives. Crusted scabies is often treated with topical permethrin and three doses of oral ivermectin^{20,22}, though additional ivermectin doses can be considered in severe cases, and some countries recommend permethrin or oral ivermectin, rather than combination treatment.¹⁹ Patients are generally rechecked for mites at weekly intervals and topical permethrin treatment often involves more than one application at 1 to 2 week intervals.²² Pruritus may persist for 2 to 4 weeks after successful treatment of infection.^{20,22} Environmental cleaning of items such as clothing, bedding, and towels is also recommended. Lindane is not recommended.^{19,20,22}

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

After review, 37 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Cochrane-ivermectin and permethrin for treating scabies^{1,2}

Cochrane conducted a 2018 review on the use of ivermectin and permethrin for treating scabies. The literature search was conducted through April 25, 2017 and included RCTs comparing permethrin or ivermectin (topical or systemic) against each other in people with scabies of all ages. A total of 15 studies (N=1986) were included and these had a moderate risk of bias (RoB). Most studies were conducted in South Asia or North Africa. Scabies is more common in these areas and associated primarily with poverty.

Permethrin 5% cream may have a higher clearance after 1 week compared to standard dose (200 mcg/kg) oral ivermectin (65% vs. 43%, RR 0.65, 95% CI 0.54 to 0.78; 613 participants; 6 studies; low certainty evidence). By 2 weeks there is probably little to no difference in clearance between these treatments (74% vs. 68%; RR 0.91, 95% CI 0.76 to 1.08; 459 participants; 5 studies; low-certainty evidence). With 1 to 3 doses/applications of either of these agents, there may be little to no difference in complete clearance at 4 weeks (93% permethrin vs. 86% ivermectin; RR 0.92, 95% CI 0.82 to 1.03; 581 participants; 5 studies; low-certainty evidence). Comparing a single application of permethrin to a single dose of oral ivermectin at 1 week, there may be little to no difference in complete cure (73% vs. 68%; RR 0.93, 95% CI 0.74 to 1.17; 120 participants, 1 study; moderate-certainty evidence).

Oral ivermectin at standard dose compared to topical ivermectin 1% lotion probably has little to no difference in complete clearance rates after 4 weeks of treatment (97% vs. 96%; RR 0.99, 95% CI 0.95 to 1.03; 272 participants; 2 studies; moderate-certainty evidence). Similarly, permethrin cream compared to ivermectin lotion probably has little to no difference in complete clearance after 4 weeks (94% vs. 96%; RR 1.02, 95% CI 0.96 to 1.08; 210 participants; 1 study; moderate-certainty evidence). There is little to no difference in cure rate between different ivermectin doses (90% 2 doses vs 87% 1 doses; RR 0.97, 95% CI 0.83 to 1.14; 80 participants; 1 study; high-certainty evidence). While this dose comparison study was the smallest assessed, it was the most methodologically sound, leading to the higher certainty attributed to its results.

There were no withdrawals due to adverse events in the systemic ivermectin or permethrin groups (moderate-certainty evidence). There is probably little or no difference in proportion of patients with a least one adverse drug reaction (ADR) with comparing systemic ivermectin to permethrin after two weeks (55 participants, 1 study; moderate-certainty evidence), and slightly larger proportion with 1 ADR with ivermectin than permethrin (5% vs. 4%, RR 1.30, 95% CI 0.35

to 4.83; 502 participants; 4 studies; low-certainty evidence), though this was not statistically significant. Topical ivermectin results in rare and mild ADRs that were comparable to systemic ivermectin (very low-certainty evidence), and there were no withdrawals due to adverse events (62 participants; 1 study; moderate-certainty evidence). Differences in ADRs are uncertain between topical ivermectin and permethrin (very low-certainty evidence).

New Guidelines:

After review, 4 guidelines were excluded due to poor quality.

New Formulations or Indications:

Spinosad (NATROBA) 0.9% topical suspension received an expanded FDA-approved indication on 4/28/2021 for the topical treatment of scabies infestation in adult and pediatric patients 4 years of age and older.²³ This was based on results of 2 multicenter, randomized, double-blind, vehicle-controlled trials of 206 households (N=533 adults and pediatrics age 4 years and older). Efficacy was determined by complete cure rates for the primary subject (youngest infested subject in each household) at day 28 after a single application of drug or vehicle-control on day 1. Results showed a statistically significant cure rate of spinosad compared to vehicle control at day 28 in both studies (trial 1 69.8% vs. 46.5%, difference 22.7%, 95% CI 1.8% to 43.5%; trial 2 83.9% vs. 34.5%, difference 49.7%, 95% CI 36.0% to 63.5%).²³

Ivermectin (SKLICE) 0.5% lotion received prescription to over-the-counter status switch approval from the FDA on 10/27/2020. It remains indicated for the topical treatment of head lice infestation in patients 6 months of age and older.²⁴

New FDA Safety Alerts:

None

Randomized Controlled Trials:

A total of 184 citations were manually reviewed from the initial literature search. After further review, 184 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). Seven additional studies related to use of topical antiparasitic agents for treatment of rosacea were reviewed and excluded as the condition is unfunded.

NEW DRUG EVALUATION:

See **Appendix 4 for Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Abametapir is a metalloproteinase inhibitor which disrupts metalloproteinases necessary for egg hatching and louse development. It received FDA approval in June 2020 for topical treatment of head lice infestation in patients 6 months of age and older.⁴ Unlike most other agents used for head louse, abametapir has significant ovicidal activity and reapplication after 7 days is not recommended.

Abametapir was approved based on the efficacy of two identical, double-blind, VC trials in patients 6 months and older with active louse infections and no previous treatment.³ The youngest patient in each family with at least 3 live lice was considered the index subject (IS). Households (IS and all infested members) were randomized 1:1 to receive a 200 g, single-application bottle of abametapir 0.74% lotion or VC (same formulation minus abametapir). Patients or caregivers were given instructions for home application which included applying sufficient amount to achieve saturation of dry hair and rinsed out with warm water after 10 minutes. Nit combing was not allowed for 14 days before and after treatment. Infested family members of the IS were non-index subjects (NS) and received the same therapy as the IS. Language of instruction for non-primary English speakers was not described. Bottles were weighed at the initial follow-up visit and amount of product used was similar between groups. Most patients were female (85%) and white (95%), each trial having sizable Hispanic representation (80.5% and 43.5%). Average age was 7.4 to 9.8 years, approximately 89% were between 6 months and 12 years of age, and no index subjects were over 65 years.²⁵ Hair characteristics (texture, length, volume, shape) were similar between groups.²⁵ After treatment application, patients returned for follow-up visits on day 1, 7, and 14 to be assessed for presence of any live louse. Assessment was performed by trained evaluators who “performed systematic head louse evaluations until live lice were observed or 15 minutes had elapsed.” Training of evaluators and specific assessment technique used (e.g., visual observation, wet-combing, or dry-combing) were not detailed.

The primary and secondary endpoints were assessed using intention-to-treat (ITT) analyses. Abametapir was found to be superior to VC in the primary endpoint of IS louse-free at all study follow up visits for both study 1 (81.1% vs. 50.9%; OR 4.01; 95% CI 1.70 to 9.48; p=0.001) and study 2 (81.8% vs. 41.2%; OR 5.50; 95% CI 2.20 to 13.73; p<0.001). There were two secondary endpoints, louse free proportion in the ITT IS population at day 1 and day 7. Louse free proportion of those treated with abametapir was not different from VC at day 1 in either study (Study 1 92.5% vs 83.6%; p=0.10; Study 2 87.3% vs. 83.0%; p=0.45; OR and 95% CI not reported). Statistically significantly more patients who received abametapir were louse free at day 7 than those receiving VC (Study 1 90.6% vs 61.8%; p=0.001; Study 2 85.5% vs. 67.9%, p=0.049; OR and 95% CI not reported).

This study is limited by lack of an active comparison, given the multiple therapeutic agents available for this indication. It is unclear how blinding was maintained, or if the abametapir lotion had any substantive differences (e.g., smell, color) to the VC (same formulation without active ingredient) that may have led to unblinding of patient or trained evaluator. There is an unexpectedly high placebo response rate which the authors attributed to ovicidal activity of unknown mechanism seen with the VC an *in vitro* study of VC (55% ovicidal efficacy) versus water control (10-20% ovicidal efficacy). This does not adequately explain the high placebo response, a phase 2 study with *in vivo* application abametapir lotion or VC showed similar VC ovicidal efficacy without correspondingly high percentages of louse free participants in the VC group.²⁶ The method of detection and training of the evaluators in all of these studies is unclear. If visual observation without combing was used for detection of live louse, then an overestimation of louse free patients in both the abametapir and VC groups may have occurred, reducing the clinical significance of the results.

Clinical Safety:

All patients who received study medications (IS and NS) were included in safety analysis. One serious adverse event was noted in a 34-year-old female patient in study 1 who was hospitalized with renal failure, which was judged to be unrelated to the study medication. Erythema (4%), rash (3.2%), and skin burning sensation (2.6%) were the most frequently reported TEAE (see **Table 1**). Additionally, specific local AEs were monitored (see **Table 2**). No patients withdrew due to adverse events, no deaths occurred, and no other serious AEs were reported.

Table 1. Adverse Events Observed in Clinical Trials^{3,4}

Adverse Reaction	Abametapir 0.74% lotion N=349 Subjects (%)	Vehicle-Control N=350 Subjects (%)
Erythema	14 (4.0)	6 (1.7)
Rash	11 (3.2)	8 (2.3)
Skin burning sensation	9 (2.6)	0 (0.0)
Contact dermatitis	6 (1.7)	4 (1.1)
Vomiting	6 (1.7)	2 (0.6)
Eye irritation	4 (1.2)	2 (0.6)
Hair color changes*	3 (1.0)	0 (0.0)

*All resolved by day 7

Table 2. Monitored Local Adverse Reactions with New Onset on Day 1 Post-Treatment⁴

Adverse Reaction	Abametapir 0.74% lotion Subjects (%)*	Vehicle-Control Subjects (%)*
Scalp Erythema/Edema	11 (3.2)	5 (1.4)
Scalp Pruritus	2 (1.4)	1 (0.7)
Eye Irritation	6 (1.7)	5 (1.4)

* Denominators dependent upon number of subjects with symptom absent at baseline.

Risk of adverse reactions and safety are unknown for repeat administration. Safety in patients who are pregnant, lactating, less than 6 months old, over 65 years old, and patients with underlying skin conditions is unknown. There is potential for drug interactions due to inhibition of multiple cytochrome P450 pathways, including 3A4, 2B6, and 1A2, and use of abametapir should not occur within two weeks of use of drugs which are substrates of these enzymes. This product contains benzyl alcohol, associated with neonatal “gasping syndrome”, and should not be used in ages below FDA approval.⁴ Potential drug interactions due to high protein binding of the absorbed drug product are unknown.

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Eradication of infestation
- 2) Reduction in need for rescue treatment
- 3) Serious adverse events
- 4) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Louse free at all post treatment days (1, 7, 14)

Table 3. Pharmacology and Pharmacokinetic Properties.⁴

	<p>water. Nit combing not permitted for 14 days before or after treatment.</p> <p>All family members with head lice enrolled.</p> <p>Youngest member designated as IS.</p> <p>Other members with at least 1 live head louse designated NS.</p>	<p>-investigational agent during 30 days before enrollment</p> <p>-visible scalp or skin condition not related to louse infestation (e.g. eczema or atopic dermatitis)</p> <p>-prior reaction to permethrin product</p> <p>-refusal/ineligibility of any family member excludes whole family</p>					<p>details in publication (OR, 95% CI, non-significant p values).</p> <p><u>Other Bias: (High)</u> Most authors had significant conflicts of interest or were employed by Hatchtech Pty Ltd. Funding for studies provided by Hatchtech Pty Ltd.</p> <p>Applicability:</p> <p><u>Patient:</u> Good representation of females, children, white, and Hispanic patients. Other ethnicities, men, and those considered “unhealthy” under represented. Exclusion of patients with failure of other agents, underlying skin conditions (e.g. eczema, atopic dermatitis), reactions to permethrin, or age less than 6 months (age due to lack of data and benzyl alcohol in formulation) limit applicability in those populations.</p> <p><u>Intervention:</u> Appropriate</p> <p><u>Comparator:</u> Comparison to standard of care would be more appropriate in this condition.</p> <p><u>Outcomes:</u> Appropriate</p> <p><u>Setting:</u> 7 sites across US; California (2), Florida, Nevada, Ohio, Tennessee, and Texas.</p>	
<p>2. Bowles VM et al.³</p> <p>See 2 above</p> <p>Study 2 NCT02062060</p> <p>Ha03-002</p>	See above	<p><u>Demographics of IS:</u></p> <p>1. Mean age (± SD) 9.8 ± 10.5 y Range 1.6 to 58.5 y</p> <p>2. Mean age (± SD) 7.8 ± 7.7 y Range 1.1 to 56.9 y</p> <p>-84.3% female -43.5% Hispanic -94.4% white</p> <p>See above for inclusion/exclusion</p>	<p>IS n=108 NS n=217</p> <p><u>ITT IS:</u></p> <p>1. 55 2. 53</p> <p><u>Safety</u> See above</p> <p><u>Attrition</u> See above</p>	<p><u>Primary Endpoint:</u></p> <p>IS Louse-free at all follow up visits (Day 1, 7, 14); ITT</p> <p>1. 81.8% 2. 47.2% OR 5.50 (95% CI, 2.20 to 13.73) P<0.001</p> <p><u>Secondary Endpoints:</u></p> <p>IS Louse-Free Day 1; ITT</p> <p>1. 87.3% 2. 83.0% P=0.45 (FDA) OR, CI not reported</p> <p>IS Louse-Free Day 7; ITT</p> <p>1. 85.5% 2. 67.9%</p>	34.6%/3	See above	See above	<p>Risk of bias: See above</p> <p>Applicability: See above; note patient population in this study has fewer overall Hispanic patients than seen in above study. Setting: 7 sites across US; Arizona, California, Florida, Mississippi, North Carolina, Tennessee, and Utah.</p>

				P=0.049 ³ P=0.025 ²⁵ OR, CI not reported				
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Abbreviations: AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; DB= double-blind; IS = index subject; ITT = intention to treat; m = months; MC = multi-center; mITT = modified intention to treat; LOCF = last observation carried forward; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-index subject; OR = odds ratio; PP = per protocol; SC = single center; SD = standard deviation; TEAE = treatment emergent adverse event; US = United States; VC = vehicle-control; y = years.

References:

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2. Rosumeck S, Nast A, Dressler C. Evaluation of Ivermectin vs Permethrin for Treating Scabies-Summary of a Cochrane Review. *JAMA Dermatology*. 2019;155(6):730-732.
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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL	OTC
permethrin	ELIMITE	TOPICAL	CREAM (G)	Y	F
permethrin	PERMETHRIN	TOPICAL	CREAM (G)	Y	F
permethrin	LICE KILLING	TOPICAL	LIQUID	Y	O
permethrin	LICE TREATMENT	TOPICAL	LIQUID	Y	O
permethrin	PERMETHRIN	TOPICAL	LIQUID	Y	O
piperonyl butox/pyrethr/permet	LICE SOLUTION	TOPICAL	KIT	Y	O
piperonyl butoxide/pyrethrins	VANALICE	TOPICAL	GEL (ML)	Y	O
piperonyl butoxide/pyrethrins	LICE KILLING	TOPICAL	SHAMPOO	Y	O
piperonyl butoxide/pyrethrins	LICE TREATMENT	TOPICAL	SHAMPOO	Y	O
crotamiton	EURAX	TOPICAL	CREAM (G)	N	F
crotamiton	CROTAN	TOPICAL	LOTION	N	F
crotamiton	EURAX	TOPICAL	LOTION	N	F
ivermectin	IVERMECTIN	TOPICAL	LOTION	N	F
ivermectin	SKLICE	TOPICAL	LOTION	N	F
lindane	LINDANE	TOPICAL	LOTION	N	F
lindane	LINDANE	TOPICAL	SHAMPOO	N	F
malathion	MALATHION	TOPICAL	LOTION	N	F

malathion	OVIDE	TOPICAL	LOTION	N	F
spinosad	NATROBA	TOPICAL	SUSPENSION	N	F
spinosad	SPINOSAD	TOPICAL	SUSPENSION	N	F
sulfur	SULFUR	TOPICAL	OINT. (G)	N	O

Appendix 2: Abstracts of Comparative Clinical Trials
None

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 6, 2021

<input type="checkbox"/> # ▲ Searches	Results	Type	Actions	Annotations
<input type="checkbox"/> 1 abametapir.mp.	5	Advanced	Display Results More ▾	
<input type="checkbox"/> # ▲ Searches	Results	Type	Actions	Annotations
<input type="checkbox"/> 1 Permethrin/ad, ae, pk, pd, tu, to [Administration & Dosage, Adverse Effects, Pharmacokinetics, Pharmacology, Therapeutic Use, Toxicity]	1174	Advanced	Display Results More ▾	
<input type="checkbox"/> 2 Piperonyl Butoxide/ad, ae, pk, pd, tu, to [Administration & Dosage, Adverse Effects, Pharmacokinetics, Pharmacology, Therapeutic Use, Toxicity]	584	Advanced	Display Results More ▾	
<input type="checkbox"/> 3 crotamiton.mp.	177	Advanced	Display Results More ▾	
<input type="checkbox"/> 4 Ivermectin/ad, ae, pk, pd, tu, to [Administration & Dosage, Adverse Effects, Pharmacokinetics, Pharmacology, Therapeutic Use, Toxicity]	5627	Advanced	Display Results More ▾	
<input type="checkbox"/> 5 lindane.mp.	2677	Advanced	Display Results More ▾	
<input type="checkbox"/> 6 Malathion/ad, ae, pk, pd, tu, to [Administration & Dosage, Adverse Effects, Pharmacokinetics, Pharmacology, Therapeutic Use, Toxicity]	1371	Advanced	Display Results More ▾	
<input type="checkbox"/> 7 spinosad.mp.	915	Advanced	Display Results More ▾	
<input type="checkbox"/> 8 Sulfur/ad, ae, pk, pd, tu, th, to [Administration & Dosage, Adverse Effects, Pharmacokinetics, Pharmacology, Therapeutic Use, Therapy, Toxicity]	1476	Advanced	Display Results More ▾	
<input type="checkbox"/> 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	13517	Advanced	Display Results More ▾	
<input type="checkbox"/> 10 limit 9 to (english language and yr="2016 -Current" and (adaptive clinical trial or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	221	Advanced	Display Results More ▾	

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XEGLYZE (abametapir) lotion, for topical use

Initial U.S. Approval: 2020

INDICATIONS AND USAGE

XEGLYZE is a pediculicide indicated for the topical treatment of head lice infestation in patients 6 months of age and older. XEGLYZE should be used in the context of an overall lice management program:

- Wash (with hot water) or dry-clean all recently worn clothing, hats, used bedding and towels
- Wash personal care items such as combs, brushes and hair clips in hot water
- Use a fine-tooth comb or special nit comb to remove dead lice and nits (1)

DOSAGE AND ADMINISTRATION

- For topical use only. Not for oral, ophthalmic, or intravaginal use. (2)
- Shake well before use. (2)
- Apply XEGLYZE to dry hair in an amount sufficient (up to the full content of one bottle) to thoroughly coat the hair and scalp. Avoid contact with eyes. (2)
- Massage XEGLYZE into the scalp and throughout the hair; leave on the hair and scalp for 10 minutes and then rinse off with warm water. (2)
- Treatment with XEGLYZE involves a single application. Discard any unused product. Do not flush contents down sink or toilet. (2)

DOSAGE FORMS AND STRENGTHS

Lotion: 0.74% [weight by weight]. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- *Risk of Neonatal Benzyl Alcohol Toxicity:* Systemic exposure to benzyl alcohol has been associated with serious adverse reactions and death in neonates and low birth-weight infants. Safety and effectiveness in pediatric patients below the age of 6 months have not been established. Use is not recommended in pediatric patients under 6 months of age because of the potential for increased systemic absorption. (5.1)
- *Risk of Benzyl Alcohol Toxicity from Accidental Ingestion:* Administer only under direct supervision of an adult. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence of $\geq 1\%$) were erythema, rash, skin burning sensation, contact dermatitis, vomiting, eye irritation, pruritus, and hair color changes. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Dr. Reddy's Laboratories, Inc., at 1-888-966-8766 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

For 2 weeks after XEGLYZE application, avoid taking drugs that are substrates of CYP3A4, CYP2B6 or CYP1A2. Otherwise, avoid use of XEGLYZE. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2020

Appendix 5: Key Inclusion Criteria

Population	Patients with louse infestation, patients with scabies
Intervention	Drugs listed in Appendix 1
Comparator	Drugs listed in Appendix 1, oral ivermectin, or placebo
Outcomes	Louse free, Scabies free, Infestation eradication, reinfestation, secondary bacterial infections
Timing	Days to months
Setting	Outpatient