Division Director Summary Review for Regulatory Action

Date	August 23, 2016
From	Kendall A. Marcus, M.D.
Subject	Division Director Summary Review
NDA/BLA # Supplement #	NDA 206966
Applicant	Dr. Reddy's Laboratories
Date of Submission	September 14, 2015
PDUFA Goal Date	September 14, 2016
Proprietary Name / Non-Proprietary Name	XEGLYZE/abametapir
Dosage Form(s) / Strength(s)	Lotion, 0.74%
Applicant Proposed Indication(s)/Population(s)	[redacted] (b) (4) indicated for the topical treatment of head lice infestation [redacted] (b) (4) in patients 6 months of age and older. (b) (4)
Action/Recommended Action for NME:	*Complete Response*
Approved/Recommended Indication/Population(s) (if applicable)	*Treatment of head lice infestation in patients 6 months of age and older*

Xeglyze (abametapir) Review Team:

Discipline	Reviewer	Team Leader
Clinical	Kevin Clark	Gordana Diglisic
Stats	Carin Kim	Mohamed Alosh
Clin Pharm	Donny Tran	Dennis Bashaw
Nonclinical	Jill Merrill	Barbara Hill
OSI	Roy Blay	Janice Pohlman

Maternal Health	Christos Mastroyannis	Tamara Johnson
Pediatrics	Erica Radden	Donna Snyder
OPDP	Tara Turner	Melinda McLawhorn
PLT	Rowell Medina	Barbara Fuller
Product Quality		
DS	Xavier Ysern	Donna Christner
DP	Bhavishya Mittal	Moo-Jhong Rhee
Process	Tony (Yaodong) Huang	Nallaperumal Chidambaram
Micro	Eric Adeeku	Jesse Wells
Facility	Quallyna Porte	Christina Capacci-Daniel
ATL	Yichun Sun	Moo-Jhong Rhee
EA	Raanan Bloom	Scott Furness
RBPM	Maria Cowan	

I. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Pediculus humanus capitis, known as the head louse, is an obligate ectoparasite that feeds exclusively on human blood. The average life span of a head louse from the time the nit is laid until the adult louse dies is thirty days. The head louse does not have wings or legs capable of jumping, so they are transferred only through close contact between individuals. Head-to-head contact is by far the most common route of lice transmission. While the head louse feeds up to 4-5 times a day, they are capable of living off the head for periods up to 48 hours. The head louse is a distinct species from the body louse and pubic louse and is generally not considered to be a vector of other diseases.

Visualization of a live louse in the hair or on the scalp is required to establish that an individual has an active infection. Pruritis, and erythema and excoriations of the scalp are common signs and symptoms of lice infestation. Pruritis is usually the first manifestation of head lice infestation and results from an allergic reaction to lice saliva injected during feeding. Lice have a predilection for the nape of the neck and the post-auricular area of the scalp so excoriations and nits may be concentrated in those areas.

In the United States, roughly 6-12 million people, predominantly children, are treated each year for head lice. Children between the ages of 3 and 11 years are the most frequently infested group and females are more frequently affected.

Currently available over-the counter (OTC) treatments include permethrin and pyrethrins with piperonyl butoxide, although resistance to pyrethroids is common. Products available by prescription include Lindane shampoo 1%; Ovide (malathion) lotion, 0.5%; Ulesfia (benzyl alcohol) lotion, 5%; Natroba (spinosad) topical suspension, 0.9% and Sklice (ivermectin) lotion, 0.5%. Mechanical measures aimed at eradication include combing with a lice comb or shaving of the scalp.

Certain biologic functions of the louse, including digestion of the blood meal, hatching of the nit and molting utilize metalloproteinase enzymes. Abametapir, the active ingredient in Xeglyze lotion is a metalloproteinase inhibitor from the class of bipyridinium molecules. The proposed dosing of Xeglyze lotion is a single, 10-minute application of an amount sufficient to saturate the hair and scalp, followed by rinsing with water.

Two pivotal trials were submitted in support of the efficacy of Xeglyze. Trials Ha03-001 (Trial 001) and Ha03-002 (Trial 002) enrolled 704 subjects, 6 months of age and older, with head lice infestation. All subjects received a single application of either Xeglyze lotion or vehicle control. For the evaluation of efficacy, the youngest subject from each household was considered to be the index subject of the household (N=216). A significantly greater proportion of index subjects who received Xeglyze lotion demonstrated success on the primary endpoint of the proportion of index subjects who are lice free at all follow-up visits through Day14 compared to subjects who received vehicle.

Adverse reactions that occurred in at least 1% of subjects in the Xeglyze lotion group and at a greater frequency than in the vehicle group include erythema (4%), rash (3.2%), burning sensation (2.6%), contact dermatitis (1.7%), vomiting (1.7%), scalp pruritis (1.4%), and hair color changes (1%). These adverse reactions were all mild to moderate in severity and reversible. No differences in the frequencies of adverse reactions were observed across all age groups.

The temporal relationship of the application of Xeglyze lotion and the onset of vomiting in 4 of the 6 subjects who reported vomiting make the potential association of the event to Xeglyze lotion unlikely at best. However, because the half-life of abametapir in adults is 21 hours and the half-life of the carboxyl metabolite is about 71 hours, a relationship to study drug cannot be excluded.

Hair color changes represent a unique adverse event related to the mechanism of action of abametapir, which chelates metal cations such as iron and zinc. In the presence of the ferrous (Fe+2) ion, abametapir forms a water-soluble pink/red colored complex at iron concentrations as low as 1 ppm. Iron is commonly found in both well and tap water at varying concentrations. Pink/red hair discoloration which resolved within 7 days was reported in a total of 3 subjects treated with Xeglyze lotion 10 minute applications. Hair discoloration lasting approximately 2.5 months was also reported in 1 subject in a Phase 1 trial who applied Xeglyze lotion for one hour.

The requirement to evaluate this product in infants below the age of 6 months is waived because benzyl alcohol, which is one of the excipients, is known to cause neonatal gasping syndrome. Product labeling contains a warning about the risk of neonatal gasping syndrome.
Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not required.

Based on a review of the application, manufacturing capability, and inspectional documents of Dr. Reddy's Labs Unit VI (FEI 3002949085), the facility review team from the Office of Process and Facilities (OPF) determined that this facility is not considered acceptable to manufacture the drug substance for this application. Deficiencies were noted in laboratory control records, computerized systems, batch production and control records, document control system, training records, process validation, specification failure investigations, water standards and personnel hygiene. Therefore, based on deficiencies noted in product quality, a complete response will be issued.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Head lice is a common infection in the United States that affects 6-12 million people, primarily children, each year. Head lice infestation has a significant impact on affected households in terms of school and work absences, anxiety, and embarrassment. While multiple treatments are currently available for treatment, resistance is increasing to some products.	Head lice is a common disease of childhood that can have substantial impact on productivity in terms of days missed from work and on learning in terms of school days missed. Multiple treatment options increase the likelihood that effective options will be available to households.
Current Treatment Options	• Currently available over-the counter (OTC) treatments include permethrin and pyrethrins with piperonyl butoxide, although resistance to pyrethroids is common. Products available by prescription include Lindane shampoo 1%; Ovide (malathion) lotion, 0.5%; Ulesfia (benzyl alcohol) lotion, 5%; Natroba (spinosad) topical suspension, 0.9% and Sklice (ivermectin) lotion, 0.5%. Mechanical measures aimed at eradication include combing with a lice comb or shaving of the scalp.	Multiple treatments options are currently available, although resistance to some is increasing.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Two Phase 3 randomized, double-blind, multicenter, vehicle-controlled trials were submitted in support of the efficacy of Xeglyze (abametapir) lotion, 0.74%. The primary objective of each trial was to evaluate the efficacy of at-home administration of a single application of abametapir lotion on the index subject of a household. Trial subjects were enrolled by household. The index subject was defined as the youngest member of the household and had to have at least 3 live lice. All other members of the household needed to have at least 1 live louse identified. Households were enrolled at 7 centers located in the United States. In both trials, abametapir lotion was statistically superior to vehicle lotion ($p \leq 0.001$) for the primary endpoint of the proportion of lice-free index subjects at Day 14.	Efficacy was convincingly demonstrated in two adequate and well-controlled clinical trials under conditions of actual use.
Risk	• Adverse reactions that occurred in at least 1% of subjects in the Xeglyze lotion group and at a greater frequency than in the vehicle group include erythema (4%), rash (3.2%), skin burning sensation (2.6%), contact dermatitis (1.7%), vomiting (1.7%), eye irritation (1.2%), and hair color changes (1%). These adverse reactions were all mild to moderate in severity and reversible. No differences in the frequencies of adverse reactions were observed across all age groups.	The safety profile has been adequately characterized. Observed adverse reactions were mild to moderate in severity and reversible.
Risk Management	• Professional and patient labeling adequately convey observed adverse reactions and the potential adverse reactions of neonatal gasping syndrome and accidental benzyl alcohol ingestion. The product is recommended for single use in order to minimize the potential risk of accidental ingestion.	Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not required.

1. Background

Pediculus humanus capitis, known as the head louse, is an obligate ectoparasite that feeds exclusively on human blood. The average life span of a head louse from the time the nit is laid until the adult louse dies is thirty days. The head louse does not have wings or legs capable of jumping, so it is transferred only through close contact between individuals. Head-to-head contact is by far the most common route of lice transmission. While the head louse feeds up to 4-5 times a day, it is capable of living off the head for periods up to 48 hours. The head louse is a distinct species from the body louse and pubic louse and is generally not considered to be a vector of other diseases.

Visualization of a live louse in the hair or on the scalp is required to establish that an individual has an active infection. Pruritis, and erythema and excoriations of the scalp are common symptoms and signs of lice infestation. Pruritis is usually the first manifestation of head lice infestation and results from an allergic reaction to lice saliva injected during feeding. Lice have a predilection for the nape of the neck and the post-auricular area of the scalp so excoriations and eggs may be concentrated in those areas.

In the United States, roughly 6-12 million people, predominantly children, are treated each year for head lice. Children between the ages of 3 and 11 years are the most frequently infested group and females are more frequently affected.

Currently available over-the counter (OTC) treatments include permethrin and pyrethrins with piperonyl butoxide, although resistance to pyrethroids is common. Products available by prescription include Lindane shampoo 1%; Ovide (malathion) lotion, 0.5%; Ulesfia (benzyl alcohol) lotion, 5%; Natroba (spinosad) topical suspension, 0.9% and Sklice (ivermectin) lotion, 0.5%. Mechanical measures aimed at eradication include combing with a lice comb or shaving of the scalp.

Certain biologic functions of the louse, including digestion of the blood meal, hatching of the nit and molting utilize metalloproteinase enzymes. Abametapir, the active ingredient in Xeglyze lotion, 0.74% is a metalloproteinase inhibitor from the class of bipyridinium molecules. The proposed dosing of Xeglyze lotion is a single, 10-minute application of an amount sufficient to saturate the hair and scalp, followed by rinsing with water.

2. Product Quality

For detailed information about the product quality review of this application, please see reviews completed by Xavier Ysern, PhD.; Branch II; Division of New Drug API/ONDP; dated December, 29, 2015; Bhavishya Mittal, PhD; Branch V; Division of New Drug Products II/ONDP; dated April 18, 2016; Yaodong (Tony) Huang, PhD; Branch VIII, Division of Process Assessment III/OPF dated March 1, 2016; Quallyna Porte, Biologist, OPQ/OPF/DIA/BII dated April 12, 2016; Vidula Kolhatkar, PhD, Branch II, Division of Biopharmaceutics/ONDP dated April 12, 2016; Eric Adeeku, PhD, Branch I, Division of Microbiology Assessment/OPF, Raanan Bloom, PhD, Environmental Assessment Team/ONDP.

Xeglyze lotion, 0.74% contains abametapir as the active ingredient. The chemical name of abametapir is: 5, 5'-dimethyl-2, 2'-bipyridinyl. The identity, strength, purity and quality of the drug substance are deemed assured by the drug substance specification. Drug substance potential impurities have been well characterized and adequately controlled.

(b) (4). The expiration dating period of 24 months is recommended for the drug product when stored at controlled room temperature based on long-term and accelerated stability data obtained from 3 registration batches of the drug product, and 6 supportive batches of the drug product. The Environmental Assessment (EA) team finds that the NDA applicant's request for a categorical exclusion from an EA acceptable.

Accidental ingestion of Xeglyze lotion, particularly by children, poses a safety concern because of the benzyl alcohol excipient. During the drug development program, the Agency advised the applicant to choose a container/closure design for commercialization which is more in line with topical products, and refrain from using a design which is typical for oral liquids. (b) (4) therefore, the applicant selected a USP Type (b) (4) amber glass bottle (b) (4)

Final packaging for Xeglyze lotion consists of a PVC safety-coated round amber glass bottle affixed with a white polypropylene child resistant cap featuring a tri-foil inner liner. Each bottle contains about 7 oz. or 210 mL (200 g) of the lotion.

Based on a review of the application, manufacturing capability, and inspectional documents of Dr. Reddy's Labs Unit VI (FEI 3002949085), the facility review team from the Office of Process and Facilities (OPF) determined that this facility is not considered acceptable to manufacture the drug substance for this application. Deficiencies were noted in laboratory control records, computerized systems, batch production and control records, document control system, training records, process validation, specification failure investigations, water standards and personnel hygiene. Therefore, a Complete Response is recommended from the OPQ perspective.

3. Nonclinical Pharmacology/Toxicology

For full details of the pharmacology/toxicology review of this application, please see the review completed by Dr. Jill Merrill, pharmacology/toxicology reviewer. This application is considered approvable from the pharmacology/toxicology perspective.

Abametapir, the active pharmaceutical ingredient in Xeglyze lotion, 0.74%, is a metalloproteinase inhibitor, which exerts its inhibitory effects by chelating metal cations at the active center of metalloproteinases that are critical to louse egg development, hatching and survival of the head louse.

The conducted nonclinical studies greatly exaggerated the expected exposure under clinical conditions of use. Drug-related nonclinical effects observed after extended repeat testing would not be a cause for concern under the expected clinical conditions of use, which would be one time use on the scalp or hair for 10 minutes. Key findings of the non-clinical review are summarized here.

Dermal effects associated with topical administration of Xeglyze lotion in a 28-day repeat-dose dermal study in minipigs included erythema and flaking and were associated with histological observations of epidermal hyperplasia, hyperkeratosis, erosion and/or ulceration. These effects were dependent on dosing parameters (i.e., strength, frequency and contact time) and were reversible. Systemic effects included tremors, decreased activity and decreased feed consumption in both males and females. Reversibility of these systemic effects could not be assessed in males due to early termination in affected animals based on ethical considerations. Reversibility of clinical signs was demonstrated in females. No clinical signs consistent with gastrointestinal targets or smooth muscle function were observed in the clinical program. Therefore, the systemic effects noted in the dermal minipig study are not a cause for concern for the clinical single topical application of abametapir lotion which is subsequently washed off after 10 minutes.

Abametapir and abametapir-COOH, the major human metabolite, were not mutagenic in the Ames test. Abametapir caused increases in chromosome aberrations in human lymphocytes at cytotoxic concentrations and was negative in the in vivo rat micronucleus assay when administered orally at doses up to 160 mg/kg/day. The overall interpretation of the conducted genotoxicity studies is that abametapir and abametapir-COOH do not exhibit a genotoxic signal.

Abametapir has been tested for reproductive and developmental toxicology in rats and rabbits after oral administration with no significant findings independent of maternal toxicity.

4. Clinical Pharmacology

For full details of the clinical pharmacology review of this application, please see the review completed by Dr. Doanh C. Tran, PhD. From a clinical pharmacology perspective, this application is approvable.

The abametapir lotion formulation was evaluated as a 0.37% and a 0.74% strength. Based on superior efficacy and similar safety findings, the higher concentration (0.74%) was chosen for evaluation as the proposed dose for commercial development.

The pharmacokinetics of abametapir were evaluated under clinical conditions of use in lice-infested subjects from the ages of 6 months to 17 years. As expected, abametapir exposure increased as the age of subjects decreased.

The metabolic pathway of abametapir involves the sequential formation of abametapir hydroxyl and abametapir carboxyl with glucuronidation of both metabolites catalyzed by UDP glucuronosyltransferases. In vitro studies showed that abametapir is extensively metabolized, primarily by CYP1A2 and to a lesser extent CYP2B6. In vivo data suggests that unconjugated

abametapir carboxyl accounts for the vast majority of drug-related plasma exposure in humans. Abametapir carboxyl is cleared slowly from the systemic circulation and results in plasma concentration significantly higher than that of abametapir. The elimination half-life of abametapir carboxyl has not been well characterized but is estimated to be about 71 hours or longer.

Benzyl alcohol is an excipient in the formulation of Xeglyze lotion, 0.74%. Because systemic exposure to benzyl alcohol can lead to neonatal gasping syndrome, serum benzyl alcohol levels were measured following application of the lotion to assess this risk. In the two clinical trials in which benzyl alcohol levels were measured, a minority of subjects (7/39) had a single measurable concentration of benzyl alcohol only at 30 minutes or one hour post dose; the levels observed were about 30-200 fold lower than a level reported to be associated with neonatal gasping syndrome. The observed concentrations do not appear to pose a safety concern.

The clinical pharmacology reviewer recommends two postmarketing requirements to further evaluate the clinical pharmacology of Xeglyze lotion, 0.74%; a maximal use pk trial in pediatric subjects 6 months to 3 years 11 months of age, and a clinical trial to evaluate the potential inhibitory activity of cytochrome P450 3A4.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

For a complete review of the statistical analyses of efficacy for this application, see the statistical review by Dr. Carin Kim. From a statistical perspective, this application is approvable. The applicant provided convincing demonstration of efficacy in the clinical trials described below.

Two Phase 3 randomized, double-blind, multicenter, vehicle-controlled trials were submitted in support of the efficacy of Xeglyze lotion, 0.74%. The primary objective of each trial was to evaluate the efficacy of at-home administration of a single application the lotion for the treatment of head lice. Trial subjects were enrolled by household. For a household to be enrolled, the index subject needed to be the youngest member of the household and have at least 3 live lice. All other members of the household needed to have at least 1 live louse identified. The agreed upon primary endpoint was the proportion of index subjects who were lice free at all follow-up visits through Day 14. Households were enrolled at 7 centers located in the United States.

Baseline demographics and characteristics were consistent with known infection patterns of head lice. About 85% of index subjects were females between the ages of 6 months and 12 years and over 90% were white. All subjects had nits and all but 1 vehicle subject had 3 live lice present at baseline.

In both trials, Xeglyze lotion was statistically superior to vehicle lotion ($p \leq 0.001$) for the primary endpoint of the proportion of lice-free index subjects at Day 14. For the secondary

endpoints of the proportion of lice-free subjects at Day 1 and at Day 7, while the results were not statistically significant at Day 1, they were at Day 7. Findings for the intent-to-treat (ITT) analysis and the per protocol analysis were similar. ITT efficacy results are reported in Table 1.

Table 1: Proportion of Lice-free Index Intent to Treat (index ITT) Subjects at Day 14 (Primary Endpoint) and at Days 1, 7 (Secondary Endpoints)

	Trial 001			Trial 002		
	Abametapir N=53	Vehicle N=55	p-value	Abametapir N=55	Vehicle N=53	p-value
Primary Endpoint (Day 14)	43 (81%)	28 (51%)	0.001	45 (82%)	25 (47%)	<0.001
Secondary endpoints						
Day 1	49 (93%)	46(1) (84%)	0.10	48 (87%)	44 (83%)	0.45
Day 7	48 (91%)	34 (62%)	0.001	47 (86%)	36 (68%)	0.025

Source: P-value from CMH test stratified by pooled sites; the protocol-specified imputation method was to impute missing as last observation carried forward (LOCF), except for missing data at Day 14 that was imputed as treatment failure.

(1) Subject (b) (6) had a missing Day 1 assessment; however, per the SAP, this subject was considered to be a success as Days 7 and 14 were treatment success.

Because the majority of the enrolled subjects were Caucasian females between the ages of 6 months and 12 years, any differences in efficacy by gender, race or age would be difficult to detect.

7. Safety

As previously noted, the applicant evaluated Xeglyze lotion, 0.74% under actual use conditions in two identical multi-center, randomized, double-blind, vehicle-controlled trials. A total of 704 subjects 6 months of age and older with head lice infestation were enrolled, of whom all but 5 subjects were confirmed to have received the study medication. Additional data collected during Phase 2 clinical trials provided supportive safety data of use of the product in a clinical setting.

The safety database under actual conditions therefore included 349 subjects treated with Xeglyze lotion and 350 subjects treated with vehicle. Of these subjects, 21 were 6 months to 4 years of age, 166 subjects were 4 to 12 years of age, 57 subjects were 12 to 18 years of age, and 105 subjects were 18 years of age or older. The size of the safety database is considered adequate to characterize adverse events.

All subjects received a single application of either Xeglyze lotion or vehicle control. The study product was administered at home by the subject or caregiver (Day 0). The subjects were instructed to apply study product to dry hair in an amount sufficient (up to the full content of one bottle) to thoroughly coat the hair and scalp, leave on the hair and scalp for 10 minutes and then rinse off with warm water. The subjects were evaluated in the trial center on Day 1, 7 and 14. Safety evaluation included assessment of vital signs, physical examination, active assessment of local adverse reaction (eyes and scalp), laboratory evaluation (Day 1 and 14), and recording of all adverse events (AE). Scalp irritation was assessed by the investigator at

each study visit using scales for erythema, edema, pruritus, excoriation and pyoderma. Eye irritation was also assessed and rated by the investigator at each study visit.

No subject discontinued the trials due to adverse events. No deaths were reported, and no serious adverse events attributable to study product were reported.

The most common adverse reactions observed in the Phase 3 trials were application site erythema (4%), rash (3.2%), skin burning sensation (2.6%), contact dermatitis (1.7%), vomiting (1.7%), eye irritation (1.2%), and hair color changes (0.9%).

Table 2 provides adverse reactions that occurred in at least 1% of subjects in the Xeglyze lotion group and at a greater frequency than in the vehicle group. These adverse reactions were all mild to moderate in severity and reversible. The frequencies of adverse reactions were similar across all age groups.

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Table 2: Adverse Reactions Occurring in ≥1% of the Xeglyze (abametapir) lotion, 0.74% Group and at a Greater Frequency than the Vehicle Group

Adverse Reactions	XEGLYZE Lotion N=349 Subjects (%)	Vehicle Lotion 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)

I agree that the adverse reactions listed in Table 2, with the exception of vomiting, are related to the use of Xeglyze lotion. The temporal relationship of the onset of vomiting in 4 of the 6 subjects who reported vomiting make the potential association of the event to Xeglyze lotion unlikely at best. However, because the half-life of abametapir in adults is 21 hours and the half-life of the carboxyl metabolite is about 71 hours, a relationship to study drug cannot be excluded. Of note, contact dermatitis was also observed in 2/206 healthy subjects who participated in a dermal safety trial to evaluate the potential of Xeglyze lotion to induce contact sensitization.

Hair color changes represent a unique adverse event related to the mechanism of action of abametapir, which chelates metal cations such as iron and zinc. In the presence of the ferrous (Fe+2) ion, abametapir forms a water-soluble pink/red colored complex at iron concentrations as low as 1 ppm. Iron is commonly found in both well and tap water at varying concentrations.

In the Phase 3 clinical trials, investigators reported pink/red hair discoloration in a total of 3 subjects treated with Xeglyze lotion at the same trial site in Mississippi. One subject had blond hair and the other 2 had brown hair. The lotion was applied to and left on their hair for 10 minutes as per application instructions. All events resolved within 7 days. Hair discoloration was also reported in 1 subject in a Phase 1 trial. The subject had chemically-treated blond hair. Xeglyze lotion was applied to and left on the hair for 60 minutes. This event resolved within approximately 2.5 months. It is possible that the longer persistence of discoloration than occurred in Phase 3 is a result of the much longer application time in the Phase 1 trial.

No evidence of a treatment-related effect on any clinical chemistry measurement and no clinically meaningful trends were observed across the treatment groups.

Pregnant women were not excluded from enrollment in the Phase 3 clinical trials, however, only 2 pregnant subjects were enrolled. Therefore, the Division of Pediatric and Maternal Health (DPMH) Team recommended a postmarketing clinical lactation study in lactating

women who require treatment with Xeglyze lotion, 0.74% to better characterize the amount of abametapir, abametapir carboxyl and benzyl alcohol transferred into breastmilk and any potential risk associated with breastfeeding.

8. Advisory Committee Meeting

No regulatory issues requiring advisory committee input were identified during the review of this application.

9. Pediatrics

The applicant conducted Phase 3 trials in subjects 6 months of age and older, the relevant population for head lice infestation and the population for whom the applicant seeks labeling.

The applicant requested a pediatric waiver for Xeglyze lotion, 0.74% for the pediatric study requirement for ages birth through 6 months of age because necessary studies are impossible or highly impracticable; limited data is publically available to demonstrate the prevalence of head lice infestation in infants less than 6 months of age. In addition, the applicant requested a pediatric waiver for Xeglyze lotion for subjects aged 0 – 6 months because there is evidence to suggest that there is the potential of increased systemic absorption due to a high ratio of skin surface to body mass and the potential for an immature skin barrier in pediatric subjects from birth to 6 months. The Agency's Pediatric Review Committee concurred with the Pediatric Study Plan on April 30, 2014.

Each bottle (200 g) of Xeglyze lotion, 0.74% contains (b) (4) of benzyl alcohol as a (b) (4) Benzyl alcohol 0.9% when used in flush solutions has been shown to cause severe metabolic acidosis, encephalopathy and respiratory depression with gasping leading to death in infants at doses of 99 to 234 mg/kg/day. Benzyl alcohol toxicity has been particularly associated with low birth-weight infants, because of the greater dose of benzyl alcohol relative to body weight, and because the metabolic and excretory pathways for benzyl alcohol are still immature. In two clinical trials in which benzyl alcohol levels were measured in subjects ranging in age from 3 years to adult, benzyl alcohol levels were detected in a minority of subjects (7/39) with Cmax ranging from 0.52 to 3.57 µg/ml. The levels observed were about 30-200 fold lower than a level reported to be associated with neonatal gasping syndrome. The observed concentrations do not appear to pose a safety concern.

Language regarding the associated potential for neonatal gasping syndrome will be included in the Warnings and Precautions section and the Pediatric Use subsection of the labeling.

The design of the container (an amber glass bottle selected due to (b) (4)) and viscosity of the product limited the use of additional preventive measures for accidental ingestion, such as an orifice-reducing plug, or a squeezable container with flow restrictor. Therefore, labeling will include a recommendation to administer the drug to pediatric patients only under direct adult supervision. The risk of accidental ingestion will be described in the Warnings and Precautions section of the labeling.

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10. Other Relevant Regulatory Issues

Two investigator sites were inspected in support of this application. No deficiencies were found that would preclude reliance upon the data that was submitted. The reader is referred to the Clinical Inspection Summary by Roy Blay, Ph.D.; Good Clinical Practice Assessment Branch; Division of Clinical Compliance Evaluation; Office of Scientific Investigations; dated June 16, 2016.

11. Labeling

Professional and patient labeling were reviewed and labeling was finalized following minor modifications. Important elements of labeling are as follows:

- **Indications and Usage**:

Xeglyze lotion, 0.74% is indicated for the topical treatment of head lice infestation in patients 6 months and older in the context of an overall lice management program.

- **Dosage and Administration**:

Xeglyze lotion is for topical use only. (b) (4)
Treatment with Xeglyze lotion involves a single application.

- **Warnings and Precautions**:

Systemic exposure to benzyl alcohol has been associated with serious and fatal adverse reactions including "gasping syndrome" in neonates and low birth weight infants. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth weight infants may be more likely to develop toxicity.

In order to prevent accidental ingestion in pediatric patients, Xeglyze lotion should only be administered under direct supervision of an adult.

12. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not required.

- Other Postmarketing Requirements and Commitments

Three clinical trials will be required as Postmarketing Requirements (PMRs) under Food and Drug Administration Amendments Act (FDAAA). The rationales for these PMRs are discussed in the Safety section and Pediatric section of this memo.

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1. Conduct a maximal use pharmacokinetic trial of XEGLYZE Lotion, 0.74% in 16 pediatric subjects 6 months to 3 years 11 months of age with head lice infestation to fully characterize the concentration time profile of abametapir and metabolite abametapir carboxyl.

2. Conduct a clinical trial in adult subjects to evaluate the potential for XEGLYZE Lotion, 0.74% to inhibit the activity of cytochrome P450 3A4 at several time points post dosing. The systemic exposure of abametapir and abametapir carboxyl should be similar to those observed under maximal use conditions in pediatrics. Additional drug interaction trials may be needed depending on the results of this trial.

3. A Clinical Lactation Study: A single dose, pharmacokinetic, open-label, clinical study to evaluate plasma and breastmilk concentrations of abametapir, abametapir carboxyl, and benzyl alcohol in lactating women who require treatment with XEGLYZE Lotion, 0.74%.

The applicant has agreed to conduct the following postmarketing commitment.

4. Conduct a study to evaluate the long-term storage stability of abametapir carboxyl in plasma stored at -80 ºC for duration of at least 1251 days.

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/s/

KENDALL A MARCUS
08/24/2016