Cross-Discipline Team Leader Review

Date	July 15, 2016
From	Gordana Diglisic, MD
Subject	Cross-Discipline Team Leader 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)	Treatment of head lice infestation in patients 6 months of age and older
Recommendation on Regulatory Action	*Complete Response*
Recommended Indication(s)/Population(s) (if applicable)	Treatment of head lice infestation in patients 6 months of age and older

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Head lice (Pediculosis capitis) infestation is common in United States among children 3-12 years of age; approximately 6-12 million have infestation each year.[1] Persons from all social and economic backgrounds can become infested with head lice, and infestation can reach epidemic proportions, especially among schoolchildren. Lice are transferred by close contact and possibly by sharing of hats, combs, and brushes. The major complaint of persons affected with head lice is severe pruritus of the scalp. Scratching leads to excoriation and secondary bacterial infection.[2] Although *P. humanus capitis* is not a vector of human disease and poses no significant health hazard to infested persons; head lice infestation may cause considerable social distress[3]. Pediculosis capitis may result in considerable discomfort, parental anxiety, embarrassment to the child, and unnecessary absence from school and work.

Therapeutic options for the treatment of head lice infestation include approved and unapproved drug products and mechanical measures such as combing or shaving of the scalp (the latter generally reserved for very young children because of the psychological distress that can result). Approved drug products indicated for the treatment of head lice infestation include pyrethrins with piperonyl butoxide solution/mousse (e.g. RID); 1% permethrin cream rise (e.g. NIX); 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%.

XEGLYZE (abametapir) Lotion, 0.74% is a topical product proposed for the treatment of head lice infestation in patient 6 months of age and older. Abametapir, the active ingredient in XEGLYZE Lotion, is a pediculocide in the class of metalloproteinase inhibitors. The proposed dosing regimen is a single, 10 minute application of an amount sufficient to saturate the hair and scalp, followed by rinsing with water.

Two pivotal trials, Ha03-001 and Ha03-002, enrolled 704 subjects, 6 months of age and older, with head lice infestation. For the evaluation of efficacy, the youngest subject from each household was considered to be the index subject of the household (N=216). In each of two adequate and well-controlled trials, a significantly greater proportion of subjects who received XEGLYZE Lotion, 0.74% demonstrated success on the primary endpoint of the proportion of index subjects who are lice free at all follow-up visits though Day14 compared to subjects who received vehicle.

The safety database was adequate to characterize the safety profile of XEGLYZE Lotion. Adverse reactions include local manifestations of scalp erythema (4%), rash (3.2%), skin burning sensation (2.6%), contact dermatitis (1.7%), vomiting (1.7%), eye irritation (1.2%), scalp pruritus

(1.4%), and hair color changes (1%). The adverse reactions were mild to moderate in severity and reversible. The frequencies of adverse reactions were similar across all age groups.

Prescription and patient labeling as well as routine pharmacovigilance are adequate to manage the risk of XEGLYZE Lotion in the post market milieu; a Risk Evaluation and Mitigation Strategy (REMS) is not needed. Recommended postmarketing studies include a maximal use pharmacokinetic trial of XEGLYZE Lotion, 0.74% in 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, a clinical trial in adult subjects to evaluate the potential for XEGLYZE Lotion, 0.74% to inhibit the activity of cytochrome P450 3A4, a Clinical Lactation Study and a study to evaluate the long-term storage stability of abametapir carboxyl in plasma stored at -80 ºC for a duration of at least 1251 days.

References:

[1] American Academy of Pediatrics; Pediatrics; Vol. 110 No. 3, September 2002, pp.638-643
[2] Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease, Vol. 2, 2972, 2000
[3]Angel, T. A., Nigro, J., & Levy, M. L. (2000). Infestations in the pediatric patient. Pediatric Clinics of North America, 47, 921-935.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Head lice (Pediculosis capitis) infestation is common in United States among children 3-12 years of age; approximately 6-12 million have infestation each year. • Although not severe or life-threatening, head lice infestation may cause considerable social distress. Pediculosis capitis may result in considerable discomfort, parental anxiety, embarrassment to the child, and unnecessary absence from school and work.	Head lice infestation is a common problem, and is extremely disruptive to the lives of parents and children.
Current Treatment Options	• Approved drug products indicated for the treatment of head lice infestation include pyrethrins with piperonyl butoxide solution/mousse (e.g. RID); 1% permethrin cream rise (e.g. NIX); Lindane Shampoo,1%; OVIDE (malathion) Lotion, 0.5%; ULESFIA (benzyl alcohol) Lotion, 5%; NATROBA (spinosad) Topical Suspension, 0.9% and SKLICE	There are a number of FDA-approved treatments for head lice infestation. None of these products has 100% efficacy and resistance, especially to over-the-counter pediculocides, has been reported.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(ivermectin) Lotion, 0.5%. • Pyrethrins and piperonyl butoxide are approved for children age 2 years and older, and permethrin is approved for children 2 months of age and older. OVIDE is approved for patients 6 years and older and ULESFIA, NATROBA, and SKLICE are approved for patients 6 months of age and older. • Treatment with pyrethrins with piperonyl butoxide and ULESFIA requires two application (7days apart), permethrin and NATROBA, 1-2 application (7 days apart, only if live lice present) and SKLICE, single application. • Lindane Shampoo carries a boxed warning for neurologic toxicity. It should be used with caution in infants, children, the elderly, and individuals with other skin conditions, and those who weigh < 110 lbs (50 kg) as they may be at risk of serious neurotoxicity. Lindane Shampoo is contraindicated in premature infants and individuals with known uncontrolled seizure disorders. Lindane Shampoo is indicated only in patients who cannot tolerate other approved therapies or have failed treatment with other approved therapies. • OVIDE Lotion is flammable and chemical burns may occur with its use. • ULESFIA and NATROBA contain benzyl alcohol. Their labeling carries warnings regarding benzyl alcohol toxicity ("gasping syndrome" in neonates and low birth weight infants).	Therefore, there is a need for additional therapeutic options, particularly if they are effective after only a single treatment and have an acceptable safety profile.
Benefit	• Two pivotal trials, Ha03-001 and Ha03-002, 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 subjects who received XEGLYZE Lotion, 0.74% demonstrated success on the primary endpoint of the proportion of index subjects who are lice free at all follow-up visits	The data submitted by the applicant meet the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	though Day14 compared to subjects who received vehicle.	
Risk	• The safety database was adequate to characterize the safety profile of XEGLYZE Lotion. Adverse reactions include local manifestations of scalp erythema (4%), rash (3.2%), skin burning sensation (2.6%), contact dermatitis (1.7%), vomiting (1.7%), eye irritation (1.2%), scalp pruritus (1.4%), and hair color changes (1%). The adverse reactions were mild to moderate in severity and reversible. The frequencies of adverse reactions were similar across all age groups. • In vitro studies suggest there is a potential for inhibition of cytochrome P450 (CYP) 3A4, 2B6 and 1A2 enzymes following a single application of XEGLYZE Lotion. Therefore, the potential of XEGLYZE Lotion to inhibit CYP3A4 should be further evaluated in vivo. In addition, the available pharmacokinetic information in pediatric subjects does not capture the maximum systemic concentration of metabolite abametapir carboxyl. This information is needed to assess potential for drug interaction and interpretation of results from the in vivo drug interaction trial. • There are no available data on XEGLYZE Lotion use in pregnant women and no data are available regarding the presence of abametapir in human milk or the effects of abametapir on the breastfed infant or on milk production. A postmarketing clinical lactation study is recommended in lactating women who require treatment with XEGLYZE Lotion to better characterize the amount of abametapir, abametapir carboxyl and benzyl alcohol transferred into breastmilk and any potential risk associated with breastfeeding.	The safety profile of XEGLYZE has been adequately characterized. A postmarketing study to better characterize the amount of abametapir, abametapir carboxyl and benzyl alcohol transferred into breastmilk and any potential risk associated with breastfeeding is recommended as well as studies to assess the potential of XEGLYZE Lotion to inhibit CYP3A4.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	The following PMR (1-3) and PMC (4) are recommended: 1. 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. 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%. 4. 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. Labeling: Prescription labeling adequately addresses risks identified during product development, as well as potential risk of benzyl alcohol toxicity and drug interaction. A REMS is not recommended.	Prescription and patient labeling as well as routine pharmacovigilance are adequate to manage the risk of XEGLYZE Lotion in the post market milieu; a Risk Evaluation and Mitigation Strategy (REMS) is not needed. Prescription labeling adequately addresses risks identified during product development, as well as potential risk of benzyl alcohol toxicity and drug interaction. PMRs and PMC address remaining data needs, which do not preclude determination of safety and effectiveness in patients 6 months of age and older with head lice infestation.

2. Background

XEGLYZE (abametapir) Lotion, 0.74% is a topical drug product for which the applicant seeks approval under Section 505 (b) (1) of the Federal Food Drug and Cosmetic Act for the topical treatment of head lice infestation in patients 6 months of age and older. The active ingredient, abametapir, is a pediculocide in the class of metalloproteinase inhibitors. Abametapir is a new molecular entity which is not marketed as a drug in the United States.

Treatment with XEGLYZE Lotion involves a single application. XEGLYZE Lotion should be apply to dry hair in an amount sufficient (up to the full content of one bottle) to thoroughly coat the hair and scalp. It is left on the hair and scalp for 10 minutes, and then rinsed off with warm water. XEGLYZE Lotion should be used in the context of an overall lice management program.

XEGLYZE Lotion was developed under the IND 77510, which was submitted on December 20, 2007 by Hatchtech Pty Ltd. During their development program, the applicant interacted with the Agency at two milestone meetings [PreIND Meeting (June 20, 2007), and PreNDA Meeting (January 21, 2015)]. An End-of-Phase Two Meeting was scheduled for August 1, 2012. After review of the Premeeting Communication consisting of Agency responses to questions in the briefing package, the applicant determined that the responses were sufficient and the meeting was cancelled. The Agency recommended that the applicant develop a container/closure design to reduce the risk of accidental ingestion, using a design more typical for topical products. The applicant was also advised to conduct dermal safety studies (irritation and sensitization), however, since no ingredients in drug product absorb light in the range 290-700 nm, the applicant proposal to request a waiver for the requirement to conduct the studies to evaluate photoallergy and phototoxicity of their product was found reasonable by the Agency. Since the product contains benzyl alcohol, as excipient, the applicant was advised to evaluate the systemic exposure of benzyl alcohol in the maximal use study pharmacokinetic (PK) trial planned to be conducted in pediatric subjects.

The applicant submitted Special Protocol Assessment request on October 23, 2013 for Phase 3 protocol Ha03-001. A "Special Protocol – Agreement" letter was sent to the applicant on December 4, 2013. The letter specified that the Agency agreed with the general design of the proposed Phase 3 trial (Ha03-001), including proposed study population (males or females 6 months of age or older with active head lice defined as at least 3 live lice for the index subject, and 1 live louse for the other household members), proposed dosing regimen (single application for 10 minutes), proposed primary endpoint (proportion of index subjects who are lice free at all follow-up visits though Day 14), proposed definition of ITT (all index subjects who were randomized) subjects, and primary analysis method (CMH test stratified by site). However, there were three non-agreement items, concerning the applicant's method of handling missing data, the proposed secondary endpoints, and periodic laboratory safety assessments.

In response to the SPA letter, the applicant submitted an amended Phase 3 protocol along with its Statistical Analysis Plan (SAP) which included a multiplicity adjustment plan for controlling the Type I error rate for the analysis of the two secondary endpoints. In an Advice Letter dated: October 20, 2014, the Agency reiterated its previous comments (dated: December 4, 2013; March 10, 2014) that the applicant consider a method of handling missing data consistent for the primary as well as for the secondary endpoints so that results of the clinical trial can be reasonably interpreted.

A Pre-NDA meeting was held on January 21, 2015. The content and format of the pending NDA submission were discussed. In addition, regarding the study Ha03-008, the applicant was advised that "the "ex- vivo" method of assessing ovicidal activity involves the evaluation of the hatch rate after removal of the eggs from the subject (before and after treatment). The ovicidal activity observed ex-vivo may not predict the ovicidal activity observed in- vivo. Differences in conditions (ex- vivo versus in- vivo) can make interpretation of the results challenging. The Agency stated that adequacy of the data from trial Ha03-008 to support (b) (4)

On December 29, 2015, the Agency received a notification regarding a "Change in Ownership of an Application" from Hatchtech Pty Ltd to Dr. Reddy's Laboratories, S.A.

Head lice (Pediculosis capitis) infestation is common in United States among children 3-12 years of age; approximately 6-12 million have infestation each year. Persons from all social and economic backgrounds can become infested with head lice, and infestation can reach epidemic proportions, especially among schoolchildren. Lice are transferred by close contact and possibly by sharing of hats, combs, and brushes. Symptoms of head lice infestation include pruritus, erythema, and excoriations of the scalp. Approved drug products indicated for the treatment of head lice infestation include Lindane Shampoo, 1%; pyrethrins with piperonyl butoxide solution/mousse (e.g. RID); permethrin cream rise, 1% (e.g. NIX); OVIDE (malathion) Lotion, 0.5%; ULESFIA (benzyl alcohol) Lotion 5%; NATROBA (spinosad) Topical Suspension, 0.9% and SKLICE (ivermectin) Lotion, 0,5%.

3. Product Quality

XEGLYZE (abametapir) Lotion, 0.74% contains abametapir as the active ingredient. The chemical name of abametapir is: 5, 5'-dimethyl-2, 2'-bipyridinyl. Abametapir is a white to pale yellow solid that has an empirical formula of C12H12N2 and a molecular weight of 184.24. The identity, strength, purity and quality of the drug substance are deemed assured by the drug substance specification. Drug substance potential impurities (including only observed in forced degradation studies) have been well characterized and adequately controlled. Abametapir is manufactured by Dr. Reddy's Laboratories.

The drug product, XEGLYZE (abametapir) Lotion, 0.74% is a viscous, white to off-white oil in water emulsion, the following composition:

Table 1: Drug product Composition

Component	Function	Quality Standard	Abametapir Lotion (0.74%)				
			%w/w	Amount per unit (g/bottle)	Mode of Delivery in IIG Database	Maximum Amount Listed in IIG Database (Checked By Reviewer)	Notes
Abametapir	Active	In-house	0.74	(b) (4)			
Light mineral oi (b) (4)	(b) (4)	NF		(b) (4)	Topical-Lotion	(b) (4)	Amount used is higher than that listed in IIG database
Polysorbate 20		NF			Topical-Lotion		OK
Benzyl alcohol		NF			Topical-Lotion		Amount used is higher than that listed in IIG database
Butylated hydroxytoluene		NF			Topical-Lotion		Amount used is higher than that listed in IIG database
Carbomer 980 (b) (4)		NF			Topical-Lotion		OK
Trolamine		NF			Topical-Lotion		OK
Purified water		USP					
TOTAL							

Source: Bhavishya Mittal's review, Table 1, p 38

The identity, strength, purity including microbial limits, and quality of the drug product are deemed assured by the drug product specification. (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.

XEGLYZE Lotion is packaged in a PVC safety-coated round amber glass bottle affixed with a white polypropylene child resistant cap featuring a tri-foil inner liner. Approximately 7 oz. or 210 mL (200 g) of the lotion is filled into each bottle.

However, 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 has determined that this facility is not considered acceptable to manufacture the drug substance for NDA 206966. As a result, OPF/DIA recommends withholding approval of this application.

Therefore, ***Complete Response*** is recommended for this NDA from the OPQ perspective.

The following CR language was recommended:

"During a recent inspection of the Dr. Reddy's Lab Ltd. CTO Unit VI

(FEI 3002949085) manufacturing facility for this NDA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved."

The reader is referred to the comprehensive reviews 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.

4. Nonclinical Pharmacology/Toxicology

Abametapir (5, 5'-dimethyl 2, 2'-bipyridyl) is a metalloproteinase inhibitor. Metalloproteinases have a role in physiological processes critical to egg development and survival of lice. XEGLYZE Lotion contains no novel excipients.

The following paragraphs contain excerpts from Dr. Merrill's review:

The core battery of safety pharmacology studies for abametapir has been previously reviewed under the original IND 77510. Both the respiratory and CNS function test were acceptable and demonstrated no treatment related effects of abametapir for either parameter.

A single dose oral abametapir toxicity study was conducted in rats (150, 175, 200, 250 mg/kg). Clinical signs included body tremors at all dose levels and piloerection, fast respiration and abnormal gait or convulsions at the higher dose levels. Both males dosed at 200 and 250 mg/kg died within 4 hours of dosing.

The repeat-dose toxicity of abametapir was investigated in groups of Sprague-Dawley rats (3/sex/dose) at 0 (vehicle control), 5, or 20 mg/kg/day in a 7-day intraperitoneal toxicity study (b) (4)612). Under the conditions of this study abametapir did not produce any toxic effects when compared with the vehicle control animals. A 2-week repeat-dose oral toxicity study (0 {vehicle control}, 8, 25, 75 or 100 mg/kg/day) was conducted in CD rats (b) (4)0006). The kidney and red blood cells were identified as target organs for toxicity. Under the conditions of this study the NOAEL for abametapir was determined to be 8 mg/kg/day. Abametapir was administered to juvenile rats orally for 8 weeks at oral doses of 0 (vehicle control), 5, 12, or 30 mg/kg/day beginning on PND 7 (70658). Body weight gain, crown-rump and tibial lengths, were unaffected by treatment. There were no adverse effects on the development or maturation of the central nervous system or reproductive organs. The primary effects noted in this study included decreased red blood cell parameters (associated with the pharmacological activity of

abametapir), slightly increased creatinine (1.1to 1.3-fold above control values at the end of the treatment and recovery periods), with no histopathological correlates at any dose. Although a dosing error during Week 4 precluded development of a NOAEL, no new target organs were identified.

In a 28-day repeat-dose dermal study in minipigs, abametapir lotion [0%, 0.74%, 0.74% (administered twice/day), 3.7%] was applied to approximately 10% total body surface area (0, 14.2, 28.4, 71.0/35.5 mg/kg/day). Dermal effects, associated with topical administration included erythema and flaking 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.

Abametapir and abametapir-COOH, the major human metabolite, were not mutagenic or clastogenic based on the results of two in vitro genotoxicity tests (Ames test and human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay).

The applicant has performed the complete reproductive and developmental toxicology battery for abametapir. No effects on fertility have been observed in rats following repeated oral doses of up to 75 mg/kg/day abametapir (50 times the maximum recommended human dose (MRHD) based on C_{max} comparisons). In embryofetal development studies conducted with oral administration of abametapir during organogenesis no evidence of fetal harm or malformations, independent of maternal toxicity, were observed in pregnant rats and rabbits at doses that produced exposures up to 50 times and equivalent to the MRHD in rats and rabbits, respectively. The highest dose evaluated in rabbits was limited due to maternal toxicity associated with the vehicle used in the study.

Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of XEGLYZE Lotion or abametapir because XEGLYZE Lotion is not intended for chronic use.

The reader is referred to the comprehensive review by Jill C Merrill, Ph.D. dated April 13, 2016.

There are no outstanding pharmacology-toxicology issues.

The pharmacology-toxicology reviewer, Jill C Merrill, Ph.D., recommended ***Approval*** of this application from nonclinical pharmacology/toxicology perspective (review dated April 13, 2016).

5. Clinical Pharmacology

The pharmacokinetics of XEGLYZE Lotion, 0.74% was evaluated in three pharmacokinetics (PK) trials, Trial Ha02-003, Ha03-003 and Ha03-004. Each trial enrolled subjects with head lice infestation. All subjects received treatment as a single 10 minute application of XEGLYZE Lotion, 0.74%. Pharmacokinetic samplings were carried out to 72 hours post dose in adults and 8 hours post dose in pediatrics subjects.

Trial Ha02-003 evaluated pharmacokinetics in 6 adult and 12 pediatric subjects (10 subjects: 6 to 12 years of age and 2 subjects 3 to 5 years of age).

The mean (%CV) abametapir plasma maximum concentration (C_{max}) and area under the concentration time curve from 0 to 8 hours post dose (AUC0-8h) in the adult group were 41 (66%) ng/mL and 121 (50%) ng*h/mL, respectively (Table 2). The mean (%CV) C_{max} and AUC0-8h in the pediatric group were 73 (57%) ng/mL and 264 (62%) ng*h/mL, respectively, and were higher compared to the values for adults. The mean (%CV) terminal half-life in adults was 21 (11%) hours.

Table 2: Mean (%CV) abametapir PK parameters (Ha02-003)

Group	C_{max} (ng/mL)	T_{max} [a] (h)	$T_{1/2}$ (h)	AUC0-tlast (h*ng/mL)	AUC0-inf (h*ng/mL)	AUC0-8h (h*ng/mL)
Adults (N=6)	41.0 (66%)	1.54 (0.48-.02)	21.3 (11%)	278.8 (44%)	302.5 (42%)	120.7 (50%)
Pediatrics (N=12)	72.6 (57%)	0.58 (0.42-.03)	Not calculated	263.2 (63%)	NA	263.9 (62%)

[a] Median (range)
Source: Dr. Tran review; Table 3 p10

Trials Ha03-003 and **Ha03-004** evaluated pharmacokinetics in pediatric subjects 6 months to 17 years of age. Abametapir exposure increased as the age of the subject decreased. Absorption of abametapir was rapid with a median T_{max} of 0.57 to 1.54 hours. The PK profile is similar to those seen in trial Ha02-003. The pharmacokinetic results for plasma abametapir are shown in Table 3 below.

Table 3: Abametapir pharmacokinetic parameters in subjects with head lice infestation (Ha03-003 and Ha03-004)

Study	Age Group	n	C_{max} (ng/mL) Mean (%CV)	AUC0-8h (ng*h/mL) Mean (%CV)
HA03-003	6 months to <1 year	1	418	1057
HA03-004		5	228 (50%)	688 (43%)
HA03-003	1 year to <2 years	3	209 (62%)	446 (65%)
HA03-004		8	147 (49%)	406 (37%)
HA03-003	2 years to <3 years	6	206 (66%)	633 (57%)
HA03-004		8	160 (48%)	602 (51%)
HA03-003	3 years to 17 years	12	121 (60%)	330 (49%)
HA03-004		7	52 (45%)	194 (39%)

Source: Dr. Tran review; Table 4 p11

Metabolism; abametapir hydroxyl and abametapir carboxyl

Abametapir is extensively metabolized, primarily by the cytochrome P450 enzyme CYP1A2 to a mono-hydroxylated metabolite (**abametapir hydroxyl**) and further to a mono-carboxylated metabolite (**abametapir carboxyl**). Abametapir carboxyl is cleared slowly from the systemic circulation resulting in plasma concentration significantly higher than that of abametapir. Based on data in adults (Trial Ha02-003), where samplings was carried out to 72 hours, the ratios of C_{max} and AUC0-72h between abametapir carboxyl and abametapir were about 30 and 250, respectively. Abametapir carboxyl concentration increased with decreasing age. The sampling out to 72 hours (Trial Ha02-003) did not adequately capture the full profile of abametapir carboxyl. The elimination half-life of abametapir carboxyl is estimated to be approximately (mean ± SD) 71 ± 40 hours or longer in adults. In some subjects the plasma abametapir carboxyl concentrations appears to be at a plateau out to 72 hours. The summary of PK parameters for abametapir carboxyl from the three PK trials is shown in Tables 4 to 6. The C_{max} values noted in these tables may not represent the true C_{max} because the sampling times were not adequate to capture T_{max} in all pediatric and some adult subjects.

Table 4: Abametapir carboxyl PK parameters for XEGLYZE Lotion, 0.74% from Trial Ha02-003

n	Age Group	C_{max} (ng/mL) Mean ± SD	T_{max} (hours) Median ± SD	AUC_{0-8} (ng*h/mL) Mean ± SD
6	Adults	1130 ± 397	28.7 ± 16.9	4900 ± 1680
12	2 to 12 years	2000 ± 1140	8.0 ± 0.0	11400 ± 6550

Abbreviations: n= number of subjects; SD = standard deviation.
Source: Dr. Tran review

Table 5: Abametapir carboxyl PK parameters for XEGLYZE Lotion, 0.74% From Trial Ha03-003

Age Group	n	C_{max} (ng/mL) Mean (CV%)	T_{max} (hours) Median (Range)	AUC_{0-8} (ng*h/mL) Mean (CV%)
6 to <12 months	1	9710	7.92	62408
1 to <2 years	3	3863 (41%)	7.97 (7.90 - 8.03)	24158 (30%)
2 to <3 years	6	6172 (34%)	7.99 (7.90 - 8.02)	38334 (37%)
3 to <18 years	12	3353 (58%)	7.89 (2.00 - 8.03)	21369 (64%)

Abbreviations: CV = coefficient of variation; n = number of subjects.
Source: Dr. Tran review

Table 6: Abametapir carboxyl PK Parameters for XEGLYZE Lotion, 0.74% from Trial Ha03-004

Age Group	n	C_{max} (ng/mL) Mean (%CV)	T_{max} (hour) Median (range)	AUC_{0-8} (ng*h/mL) (%CV)
6 to <12 months	1	6830	8.00 (8.00 - 8.00)	37500
1 to <2 years	2	3550 (1.8%)	5.00 (2.03 - 7.97)	24600 (0.3%)
2 to <3 years	7	4290 (46.7%)	8.00 (7.85 - 8.00)	26000 (49.5%)
3 to 17 years	7	1760 (41.9%)	8.00 (7.83 - 8.08)	10000 (46.4%)

Abbreviations: CV = coefficient of variation; n = number of subjects.
Source: Dr. Tran review

Benzyl Alcohol

Benzyl alcohol is an excipient in the formulation of XEGLYZE Lotion. Benzyl alcohol serum concentrations were assessed in PK samples from trials Ha03-003 and Ha03-004:

- In Trial Ha03-003, one of 9 evaluable subjects (13 subjects from site 02 were excluded due to inadvertent use of saline flush containing benzyl alcohol) had measurable concentrations of 0.536 and 0.726 mcg/mL at 0.5 hour and 1 hour post dose, respectively.
- In Trial Ha03-004, six of 30 subjects had measurable concentrations of 0.524, 0.664, 0.826, 0.877, 1.39, and 3.57µg/mL. Only one measurable concentration was seen in each

subject (4 of the samples were seen at 0.5 hours post dose and 2 samples were seen at 8 hours post dose).

Systemic exposure to benzyl alcohol at a concentration of ~109.2 µg/mL (1.01mmol/L) has been associated with neonatal gasping syndrome (Gershanik et al., N Engl J Med 1982; 307:1384-1388). The highest benzyl alcohol concentration observed in the trials with XEGLYZE Lotion, 0.74% is 3.57µg/mL, which is about 30 fold lower.

Distribution

Abametapir and its primary human metabolite, abametapir carboxyl, are highly bound to proteins in plasma. Abametapir is 91.3 – 92.3% bound to plasma proteins, and abametapir carboxyl is 96.0% – 97.5% bound to plasma proteins.

Extrinsic Factors

CYP inhibition potential of

- abametapir:
  - Abametapir is metabolized mainly by CYP1A2. Inhibition of this enzyme may lead to increased systemic exposure to abametapir. Abametapir reversibly inhibited the activity of CYP1A2 (Ki = 39 µM). It did not inhibit the activity of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5 at up to 40 µM. Considering the highest mean C_{max} (in subjects <1 year of age) in maximal use PK trials Ha03-003 and Ha03-004 was 1.41 µM, the [I]/Ki is <0.1 suggesting low risk of in vivo CYP inhibition.
- abametapir carboxyl:
  - In human liver microsomes studies, the results showed no significant (>30%) inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 at concentrations up to 200 µM for abametapir carboxyl. Based on highest clinically observed plasma total C_{max} of 45.3 µM (9710 ng/mL) or unbound concentration of 1.81 µM, risk of CYP inhibition for abametapir carboxyl is low.

    However, in a study with human hepatocytes to evaluate the induction potential, abametapir carboxyl showed concentration dependent inhibition of all 3 tested enzymes (CYP1A2, CYP2B6 and CYP3A4; with CYP3A4 being most sensitive) with 50% inhibition of enzyme activity at concentrations in the range of 50 – 200 µM and 50% inhibition of mRNA expression as low as in the range of 5 – 15 µM. The reason for this discrepancy between results of hepatocyte studies and microsomal studies is not clear.

CYP induction potential of

- abametapir:
  - Abametapir did not markedly (≥2-fold) induce CYP1A2, CYP2B6, or CYP3A4 activity (most cases were ≤1.4-fold except for CYP1A2) and did not markedly induce (≥20% of that elicited by the positive control) CYP1A2, CYP2B6, or CYP3A4 mRNA expression.

There was no evident of positive concentration response relationship for any enzymes tested. Thus, at up to 40 μM, abametapir is not considered an inducer of human CYP450s.

- abametapir carboxyl:
  - Abametapir carboxyl did not markedly (≥2-fold) induce CYP1A2, CYP2B6, or CYP3A4 activity and did not markedly induce (≥20% of that elicited by the positive control) CYP1A2, CYP2B6, or CYP3A4 mRNA expression. Abametapir carboxyl, at up to 200 μM, is not considered an inducer of human CYP450s.

Per Dr. Tran, although there is low risk of in vivo CYP inhibition for abametapir and low risk of CYP induction for both abametapir and abametapir carboxyl, there is a potential risk of CYP3A4 inhibition due to high and sustained plasma concentration of abametapir carboxyl following application of XEGLYZE Lotion. Therefore, the potential of XEGLYZE Lotion to inhibit CYP3A4 should be further evaluated in vivo. In addition, the available pharmacokinetic information in pediatric subjects does not capture the maximum systemic concentration of metabolite abametapir carboxyl. This information is needed to assess the potential for drug interaction and to interpret results from the in vivo drug interaction trial. This trial can be conducted post approval because the clinical trial data did not indicate safety concerns with the drug itself and the safety concerns with potential drug interaction can be temporarily addressed via labeling. See below recommendation for PMRs as well as labeling.

Method validation

The plasma samples from the human PK trials were analyzed for abametapir, abametapir hydroxyl and abametapir carboxyl using tandem mass spectrometry (LC-MS/MS) methods and benzyl alcohol by gas chromatography-mass spectrometric procedures (GC-MS). All bioanalytical methods were adequately validated.

Analysis of abametapir and benzyl alcohol in plasma samples in all clinical trials was conducted within established long term storage stability. For analysis of abametapir carboxyl, samples from trials Ha03-003 and Ha03-004 were analyzed within the demonstrated storage stability duration of 568 days. Samples from trial Ha02-003 were collected in 2011 and retained in storage for 1251 days prior to analysis for abametapir carboxyl. Therefore, there is insufficient demonstrated stability to support the analysis of abametapir carboxyl in trial Ha02-003. Dr. Tran noted that "the AUC and C_{max} for pediatric subjects (aged 3 – 12 years) in trial Ha02-003 was similar to and in between those observed for the 3 - 17 years age group in trials Ha03-003 and Ha03-004, which were analyzed within the demonstrated stability period. The same order among the 3 trials was seen for the parent abametapir. These data suggest that there were no overt degradation of abametapir carboxyl samples from trial Ha02-003 and the data may be used for review. However, the sponsor should continue to evaluate the storage stability to fully support the storage duration as a post marketing commitment." See below recommendation for PMC below.

QT study

The Applicant conducted a thorough QT study (**Ha02-005)** in healthy adults without head lice infestation. Part 1 of the trial was designed to determine the maximum well-tolerated exposure to XEGLYZE Lotion, 0.74%. Investigators applied XEGLYZE Lotion to the scalp and back of healthy adults for treatment periods of 20, 40, and 60 minutes. Application for 60 minutes proved to be well tolerated, and C_{max} values were 6 times higher than C_{max} seen in trial Ha02-003 (10 minute application, adults and children >2 years of age with head lice infestation). Therefore, investigators chose the 60 minute exposure as the supra-therapeutic exposure for Part 2, the TQT evaluation.

Based on applicant's analysis, administration of XEGLYZE Lotion, 0.74% for 60 minutes to the scalp and back in healthy adults without head lice did not prolong cardiac repolarization (QTc interval). The results of this study were reviewed by QT-IRT under IND 77510 (Dr. Qianyu Dang, June 14, 2013). Dr. Dang concurred with the applicant's conclusion. The mean observed abametapir C_{max} in this study was 432 ± 137 ng/mL, which exceeded those observed under maximal use conditions in subjects with active head lice infestation. The metabolite abametapir carboxyl C_{max} was 6010 ± 1120 ng/mL, which covered most subjects except for those <1 year of age. Therefore, the results of this study are applicable to the target population.

Clinical Pharmacology/Division of Clinical Pharmacology 3 recommendation:
"The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 206966 acceptable pending agreement on recommended labeling changes and post marketing requirements and commitments."

Post marketing Requirements:

FDAAA required safety study/clinical trial:

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.

PMR Schedule Milestones:	Final Protocol Submission:	3/14/2017
	Study/Trial Completion:	3/14/2019
	Final Report Submission:	9/14/2019

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.

PMC Schedule Milestones:	Final Protocol Submission:	09/14/2019
	Study/Trial Completion:	03/14/2020
	Final Report Submission:	09/14/2020

Post Marketing Commitments:

1. 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.

PMC Schedule Milestones:	Final Protocol Submission:	01/02/2017
	Study/Trial Completion:	01/02/2021
	Final Report Submission:	05/02/2021

Labeling recommendation:

Section 7 DRUG INTERACTION

In vitro studies suggest there is a potential for inhibition of cytochrome P450 (CYP) 3A4, 2B6 and 1A2 enzymes following a single application of XEGLYZE (b) (4). Use of XEGLYZE (b) (4) with drugs that are substrates of these enzymes may lead to increased systemic concentrations of the interacting drugs. Avoid administration of drugs that are substrates of CYP3A4, CYP2B6, or CYP1A2 within 2 weeks after application of XEGLYZE (b) (4). If this is not feasible, avoid use of XEGLYZE (b) (4) *[see Clinical Pharmacology 12.3]*.

The reader is referred to the comprehensive review by Doanh C. Tran, PhD. for a full discussion of the clinical pharmacology data (dated April 26, 2016).

I concur with the conclusions and recommendation reached by the clinical pharmacology review team.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The applicant submitted data from two identical pivotal trials, Ha03-001 (Trial 001) and Ha03-002 (Trial 002), to establish the effectiveness of their product in the treatment of head lice infestation. Trials were randomized, double-blind, multicenter, vehicle-controlled Phase 3 trials conducted in 704 subjects 6 months of age and older with head lice infestation. For the evaluation of efficacy, the youngest subject from each household was considered to be the index subject of the household (N=216). Other enrolled infested household members received the same treatment as the youngest subject and were evaluated for all efficacy and safety parameters.

Table 7 provides an overview of the pivotal Phase 3 trials.

Table 7: Clinical Study Overview for the Pivotal Trials

Study	Study Sites	Study Population	Treatment Arms	N	Dates
001 (N=108 index subjects)	7 U.S. centers	• Age ≥6 months, • At least 3 live lice for index subject defined as the youngest member in the household, and at least 1 live louse for other household members.	Abametapir	53	2/12/2014 - 6/26/2014
			Vehicle	55	
002 (N=108 index subjects)	7 U.S. centers		Abametapir	55	2/18/2014 - 6/27/2014
			Vehicle	53	

Source: Review by Dr. C. Kim; page 4; Table 2

The primary objective of each trial was to evaluate the efficacy of at-home administration of a single application of XEGLYZE Lotion, 0.74% for the treatment of head lice. Each trial consisted of the following two treatment groups: Group A: XEGLYZE Lotion and Group B: Vehicle. Randomization of subjects to treatment group was stratified by site.

The primary analysis population was the Intent-to-Treat (ITT) index subjects where ITT was defined as all index subjects who were randomized. A supportive analysis using the Per Protocol (PP) population was done and the PP was defined as all subjects in the ITT population without a significant protocol deviation.

The trials enrolled similar populations: subjects 6 months and older with head lice infestation. The majority of the enrolled index ITT subjects were female (85%) and Caucasians (95%). Approximately 95% of the index subjects were between the ages of 6 months and less than 18 years of age, and there were no index subjects ≥65 years of age. The demographics and baseline live lice and presence of nits were generally balanced across treatment arms.
Each trial enrolled and randomized a total of 108 index ITT subjects from 7 U.S. centers (53 to XEGLYZE Lotion, 55 to Vehicle and 55 to XEGLYZE Lotion and 53 to Vehicle in Trials 001 and 002, respectively). Table 8 presents the disposition of subjects for each trial. While the

discontinuation rates were similar across the treatment arms within each trial, the discontinuation rates were slightly higher in Trial 001 compared to those in Trial 002.

Table 8: Subject Disposition (Index ITT)

	Trial 001		Trial 002	
	XEGLYZE	**Vehicle**	**XEGLYZE**	**Vehicle**
Randomized	53	55	55	53
Discontinued	3 (6%)	3 (6%)	1 (2%)	1 (2%)
Adverse Events	0	0	0	0
Withdrew consent	0	3	0	0
Loss to Follow-up	3	0	1	1
Protocol violation	0	0	0	0
Other	0	0	0	0

Source: Applicant's Study Report Table 14.1.1.1

The primary endpoint was the proportion of index subjects who were lice free at all follow-up visits through Day 14 (Day 1, 7 and 14). Subjects with live lice at any time up to the final evaluation were considered treatment failures.

The protocol-specified secondary endpoints were: proportion of index subjects who are lice free at Day 1 visit and proportion of index subjects who are lice free at Day 7 visit. Note that these secondary endpoints (as not clinically meaningful) were one of the two non-agreements per the SPA letter (dated: December 4, 2013).

For the SPA-agreed upon primary efficacy analysis, the Cochran Mantel-Haenszel (CMH) test stratified by pooled sites was used. For handling of missing data, the protocol specified that last observation carried forward (LOCF) would be used except for those subjects with missing Day 14 visit that would be considered as treatment failures. The LOCF was then used as a sensitivity analysis for handling missing data for the primary endpoint.

Table 9 presents the proportion of subjects who were free of live lice at all visits Day 1 through Day 14 in Trials 001 and 002. Efficacy results for the primary endpoint were significant for both trials (p-value<0.001).

Table 9: Proportion of Index Subjects Free of Live Lice at All Visits Days 1 Through 14 After Treatment

	Trial 001	Trial 002

	XEGLYZE Lotion (N=53)	Vehicle Lotion (N=55)	XEGLYZE Lotion (N=55)	Vehicle Lotion (N=53)
Treatment Success	43 (81.1%)	28 (50.9%)	45 (81.8%)	25 (47.2%)

Source: Dr. C. Kim review; Table 7; page 10

As a supportive analysis, the primary efficacy results were analyzed using the Per Protocol (PP) population. The results from the PP analysis yielded very similar results to those of the index ITT population as 105 of the 108 index ITT subjects in Trial 001, and 106 of the 108 index ITT subjects were included in the PP population. Table 10 presents the efficacy analyses using the PP population.

Table 10: Proportion of Lice-free Per Protocol (PP) Subjects at Day 14 (Primary Endpoint), and at Days 1, 7 (Secondary Endpoints)

	Trial 001		Trial 002	
	XEGLYZE Lotion (N=52)	**Vehicle Lotion (N=53)**	**XEGLYZE Lotion (N=53)**	**Vehicle Lotion (N=53)**
Primary Endpoint (Day 14)	43 (83%)	28 (53%)	43 (81%)	25 (47%)

Source: Dr. C. Kim review: Table 8, page 10

Table 11 presents the sensitivity analysis results for the primary efficacy endpoint at Day 14 by using the last observation carried forward (LOCF) for Trials 001 and 002. The results were similar to those of the primary imputation method of imputing missing values as treatment failure. It should be noted that the amount of missing data in each trial was minimal.

Table 11: Results for the Primary Efficacy Endpoint at Day 14 with Last Observation Carried Forward (index ITT)

	Trial 001			Trial 002		
	XEGLYZE (N=53)	**Vehicle** (N=55)	**p-value**	**XEGLYZE (N=55)**	**Vehicle (N=53)**	**p-value**
MVTF [(1)]	43 (81%)	28[(1)] (51%)	0.001	45 (82%)	25 (47%)	<0.001
LOCF [(2)]	45 (85%)	29 (53%)	0.001	46 (84%)	26 (49%)	<0.001

Source: Dr. C. Kim review: Table 10, page 11; p-value based on a CMH test stratified by pooled sites.
(1) MVTF: Missing value treated as failure – primary imputation method; (2) LOCF: last observation carried forward.

Because the majority of the enrolled index ITT subjects were female (85%), and Caucasians (95%), any differences in efficacy for the male subjects, and non-Caucasians would be difficult to detect. Approximately 89% of the index subjects were between the ages of 6 months and less than 12 years of age. Therefore, any differences in efficacy for subjects 12 years of age and older would be difficult to detect.

The reader is referred to the reviews of Carin Kim, Ph.D. and Kevin Clark, M.D. for further information and additional analyses. Both Dr. Kim and Dr. Clark concluded that the data support a determination of efficacy (reviews dated April 22, 2016 and April 29, 2016).
I conclude that the applicant provided substantial evidence of effectiveness of XEGLYZE (abametapir) Lotion, 0.74% for the indication of treatment of head lice infestation in patients 6 months of age and older. In each of two adequate and well-controlled trials, a significantly greater proportion of 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 though Day14 to subjects who received vehicle.

8. Safety

The applicant conducted two identical multi-center, randomized, double-blind, vehicle-controlled trials (Trials 001 and 002) in 704 subjects 6 months of age and older with head lice infestation. In Trial 001 three hundred seventy nine (379) subjects were enrolled (187 subjects to XEGLYZE group). Four subjects from the XELGLYZE group failed to complete the trial, 3 returned on Day 1, but did not return for the Day 7 or Day 14 visits and were lost to follow-up. One subject did not return for the Day 1, nor the Day 7 and Day 14 visits. Because the investigator was unable to verify whether this subject used the study product or not, this subject was excluded from the safety population. In the Vehicle group, four subjects (4/192) withdrew consent before administration of the study product and were excluded from the safety population. In Trial 002 three hundred twenty five (325) subjects were enrolled (163 subjects to XEGLYZE group). In the XEGLYZE group, one family of 5 subjects did not return for the Day 7 or Day 14 visit and were lost to follow-up; however, because they received study product and returned on Day 1, they were included in the safety population. Therefore, safety database include 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 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 applied 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, Day 7 and Day 14. Safety evaluation included assessment of vital signs, physical examination, active assessment of local adverse reaction (eyes and scalp), laboratory evaluation (chemistry, hematology), and recording of all adverse events (AE).

None of subjects discontinue the trials (Trial 001 and 002) due to adverse events. There were no deaths reported, and no serious adverse events (SAE) attributable to XEGLYZE Lotion.

The most common adverse reactions (AR) 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 12 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. The adverse reactions were mild to moderate in severity and reversible. The frequencies of adverse reactions were similar across all age groups.

Table 12: Adverse Reactions Occurring in ≥ 1% of the XEGLYZE Lotion Group and at a Greater Frequency than in the Vehicle Group (Trials 001 and 002)

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)

During the trials, subjects were monitored for new onset of scalp erythema/edema, scalp pruritus, and eye irritation. The number and percentage of subjects who developed these local adverse reactions after treatment are presented in Table 13.

Table 13: Monitored Local Adverse Reactions with New Onset on Day 1 Post-Treatment (Trials 001 and 002)

Adverse Reactions	XEGLYZE Lotion Subjects (%)*	Vehicle Lotion 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)

* For the calculation of the percentages, the denominators are the number of subjects who did not have the monitored local adverse reaction at baseline.

Assessment of vital signs/physical examination and laboratory evaluation did not reveal unexpected safety signals.

XEGLYZE Lotion, 0.74% contains benzyl alcohol (b) (4)%) as an excipient. Systemic exposure to benzyl alcohol at concentration of ~109.2 µg/mL has been associated with gasping syndrome in neonates and low birth weight infants. The highest benzyl alcohol concentration observed in the trials with XEGLYZE Lotion, 0.74% is 3.57µg/mL, which is about 30 fold lower. However, because the minimum amount of benzyl alcohol at which toxicity may occur is not known, the risk of neonatal benzyl alcohol toxicity as well as risk of benzyl alcohol toxicity from accidental ingestion will be addressed in the product labeling. Additionally, since the safety of XEGLYZE Lotion has not been established in pediatric patients below the age of 6 months and because of the potential for increased systemic absorption, use of XEGLYZE Lotion is not recommended in pediatric patients under 6 months of age (refer to Section 5 and Section 10 of this review).

The applicant conducted two provocative dermal safety studies in a population of healthy subjects to evaluate the cumulative skin irritation and sensitization (Trial Ha03-007 and Ha03-006) potential of XEGLYZE Lotion, 0.74%. Two subjects (2/206; 0.97%) showed some evidence suggestive of sensitization. XEGYZE Lotion was more irritating than Vehicle and saline control. However, both XEGLYZE Lotion and Vehicle were less irritating than SLS 0.1% control. Phototoxicity/ Photoallergenicity studies were waived as no component of the drug product absorbs light corresponding to wavelengths of 290 to 700 nm (UVB, UVA, and visible).

Pregnant women were not excluded from enrollment in trials. A total of 2 pregnant subjects were enrolled into the Phase 3 trials (Trial 001 and 002). Both subjects completed the trial. At the time of study completion, the pregnancy was ongoing. In addition, a review of the literature revealed no data with XEGLYZE Lotion use in pregnant or lactating women. As a result, there are no available data on XEGLYZE Lotion use in pregnant women to inform a drug associated risk. Also, no data are available regarding the presence of abametapir in human milk or the effects of abametapir on the breastfed infant or on milk production. Therefore, 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. Concentrations of abametapir, abametapir carboxyl and benzyl alcohol should be assessed in maternal plasma and breastmilk so as to estimate potential infant exposure.

Post marketing Requirements:

FDAAA required safety study/clinical trial:

- 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%.

(Christos Mastroyannis, M.D. MHT, DPMH; review dated April 28, 2016).

The reader is referred to the clinical review by Dr. Kevin Clark for full review of the safety data.

9. Advisory Committee Meeting

No advisory committee meeting was necessary or held, as the application did not present novel issues which merited advisory committee input.

10. 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 children less than six months of age based on the rationale that studies are impossible or highly impracticable. Although, studies would be impracticable because the number of patients aged less than 6 months is low, it is recommended that studies in children 6 months of age and younger be waived because of safety concerns related to benzyl alcohol.

Each bottle (200 g) of XEGLYZE Lotion 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.
Therefore, language regarding the associated potential for neonatal toxicity should be included in the Warnings and Precautions section and the Pediatric Use subsection of the labeling. Furthermore, because this warning pertains to an unapproved subpopulation (i.e., patients < 6 months of age), labeling should state that safety and effectiveness have not been established in this subpopulation.

The design of the container (i.e., an amber glass bottle selected (b) (4)

Therefore, the labeling should include 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.

As discussed in the Section 5 of this review, the potential of XEGLYZE Lotion to inhibit CYP3A4 should be further evaluated in vivo. Because the available pharmacokinetic information in pediatric subjects does not capture the maximum systemic concentration of metabolite abametapir carboxyl and this information is needed to assess potential for drug interaction and interpretation of results from the in vivo drug interaction trial, a maximal use pharmacokinetic trial of XEGLYZE Lotion, 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 is required. This trial can be conducted post approval (as PMR) because the clinical trial data did not indicate safety concerns with the drug itself and the safety concerns with potential drug interaction can be temporarily addressed via labeling.

The Division of Pediatric and Maternal Health (DPMH) Team review the applicant's proposed labeling and provided labeling recommendations for the pediatric population per 21 CFR 201.57(c)(9)(iv) (review by Dr. Erica D Radden, DPMH/OND; dated April 22, 2016).

The application was presented to the Pediatric Review Committee (PeRC) on March 23, 2016. PeRC agreed with the applicant's requests for waiver for children less than six months of age.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI) audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted (review by Roy Blay, Ph.D.; Good Clinical Practice Assessment Branch/Division of Clinical Compliance Evaluation/OSI; dated June 16. 2016).

12. Labeling

The package insert conforms to the Physicians Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR).

All components of labeling were reviewed.

The proposed proprietary name, XEGLYZE, was found acceptable from a safety and misbranding perspective.

The carton and container labels were acceptable.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Prescription status, product labeling, and routine pharmacovigilance are sufficient to address the post-marketing safety of the product. A REMS was not proposed, and is not recommended.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Postmarketing Requirements (PMRs) under Food and Drug Administration Amendments Act (FDAAA):

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.

PMR Schedule Milestones:	Final Protocol Submission:	3/14/2017
	Study/Trial Completion:	3/14/2019
	Final Report Submission:	9/14/2019

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.

PMC Schedule Milestones:	Final Protocol Submission:	09/14/2019
	Study/Trial Completion:	03/14/2020
	Final Report Submission:	09/14/2020

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%.

PMR Schedule Milestones:	Final Protocol Submission:	03/14/2017
	Study/Trial Completion:	03/14/2018
	Final Report Submission:	09/14/2018

Postmarketing Commitments (PMCs)

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.

PMC Schedule Milestones:	Final Protocol Submission:	01/02/2017
	Study/Trial Completion:	01/02/2021
	Final Report Submission:	05/02/2021

The reader is referred to Section 5, 8 and 10 of this review.

14. Recommended Comments to the Applicant

"During a recent inspection of the Dr. Reddy's Lab Ltd. CTO Unit VI (FEI 3002949085) manufacturing facility for this NDA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GORDANA DIGLISIC
07/15/2016