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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	1 February 2012
From	Jill Lindstrom, MD FAAD
Subject	Cross-Discipline Team Leader Review
NDA #	202736
Applicant	Topaz Phamaceuticals
Date of Submission	7 April 2011
PDUFA Goal Date	7 February 2012
Proprietary Name	SKLICE
Established (USAN) names	ivermectin
Dosage forms	Lotion
Strength	0.5%
Proposed Indication(s)	the topical treatment of head lice infestation in patients 6 months of age and older
Recommended:	*Approval*

1. Introduction

SKLICE (ivermectin) lotion, 0.5%, 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 (b) (4) in patients 6 months of age and older. The active ingredient, ivermectin, is marketed in the United States as a 3mg tablet for the treatment of strogyloidiasis and onchocerciasis in humans (Stromectol, Merck), as well as in a variety of formulations for veterinary use. The applicant obtained right of reference from Merck to NDA 50742 Stromectol (ivermectin) tablet. This memo will summarize the findings of the multi-disciplinary review team and provide the rationale for my recommended action.

2. Background

Head lice infestation, pediculosis capitis, is a common and communicable condition in which the human head louse, *Pediculus humanus capitis*, infests the hairy scalp. The most prominent symptom of infestation is pruritus, and signs include lice observed on the scalp, nits attached to hair shafts, and erythema, and manifestations of excoriation such as crusting. Excoriation can result in secondary infection due to disruption in the epidermal barrier. Because the infestation is communicable, children diagnosed with the infestation may be precluded from attending school until they have received effective treatment. The therapeutic armamentarium for the treatment of head lice infestation includes 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 Ulesfia (benzyl alcohol) lotion, 5%; Natroba (spinosad) topical suspension, 0.9%; lindane shampoo, permethrin cream rinse, pyrethrins with piperonyl butoxide solution and mousse, and malathion lotion.

Ivermectin, a member of the avermectin class, is derived from fermentation of a soil-dwelling actinomycete, *Streptomyces avermitilis*. In invertebrates such as *Pediculus humanus capitis*, ivermectin binds to glutamate-gated chloride channels in nerve and muscle cells causing cell hyperpolarization with resultant paralysis and death. Ivermectin also interacts with the ligand-gated chloride channel γ-aminobutyric acid (GABA). In humans, GABA and glutamate nerve synapses are located in the central nervous system, but the mature blood-brain barrier is relatively impermeable to ivermectin.

3. CMC/Device

The drug substance, ivermectin, is a mixture of two avermectin components: B_{1a} and B_{1b}. The molecular formulas (and weights) of the components are $C_{48}H_{74}O_{14}$ (875.1) and $C_{47}H_{72}O_{14}$ (861.1), respectively. Physically, ivermectin is a white to yellowish-white powder that is soluble in methanol or acetone but not in water.

The drug product, SKLICE (ivermectin) lotion, is off-white to tan in color and contains 0.5% (5 mg/gm) of ivermectin. The composition is described in the following table:

Ingredient	Function	% w/w
Ivermectin	Drug Substance	0.5
Purified Water	(b) (4)	(b) (4)
Olive Oil		
Crodalan AWS*		
(b) (4)		
Oleyl alcohol		
Lanolin alcohol		
Cyclomethicone		
Shea butter		
Sorbitan tristearate		
Methylparaben		
Propylparaben		
Citric Acid		
Sodium Citrate		
(b) (4)		

Three of the excipients are novel: sorbitan tristearate, shea butter, and (b) (4) (b) (4) Crodalan AWS); the remainder are listed in the FDA Inactive Ingredients database. Dr. Jianyong Wang, the pharmacology toxicology reviewer, provided the following information about the three novel excipieints:

- Sorbitan tristearate is recognized as an indirect food additive, and is used in cosmetic products at concentrations up to 10%.
- Shea butter is a component of Atopiclair cream, a device cleared for the treatment of atopic dermatitis. Shea nut oil (from which shea butter is derived) is generally

recognized as safe as a direct human food ingredient. Shea butter is a component of many cosmetic products.

(b) (4)

The nonclinical dermal irritation study, ocular irritation study, and 2-week minipig dermal toxicology study were conducted with test article that contained the three novel excipients. Dr. Wang concluded that the applicant provided sufficient data to establish that the novel excipients are acceptable at the proposed concentrations.

The product, which contains (b) (4) water, is formulated with methylparaben, propylparaben and citric acid (b) (4) Microbial limits test is included in the finished product specifications.

The drug product is packaged into unit-dose laminate tubes with (b) (4) and peel seal, and a (b) (4) screw cap closure system. The applicant proposes to market a 4oz (117 gm) unit-dose tube, as was used in the pivotal trials, containing 585mg of ivermectin. Stability data support an expiry of 24 months.

Facilities inspections for the drug substance and drug product were completed, but the final report is pending at the time of close of this review.

The CMC reviewer, Dr. Carolyn Strasinger, concluded that the applicant provided sufficient information to assure the identity, strength, purity and quality of the drug product, and did not recommend any postmarketing commitments. She identified the absence of a final recommendation on facilities from the Office of Compliance (pending at the time of close of this review) and unresolved labeling issues (pending at the time of close of this review) which would preclude a recommendation for *Approval*.

4. Nonclinical Pharmacology/Toxicology

In a two-week repeat dose dermal toxicology studies in minipigs, no treatment-related dermal or systemic toxicity was identified. Ivermectin binds selectively and with high affinity to glutamate-gated chloride ion channels in invertebrate nerve and muscle cells, which results in increased permeability of the cell membrane to chloride ions and hyperpolarization of the cell leading to paralysis and death. At high doses, oral ivermectin is neurotoxic and causes tremor, depression, ataxia, paresis, paralysis and death (depending on test species). Ivermectin was negative for mutagenicity in the Ames test, the mouse lymphoma cytotoxicity and mutagenicity assays, or in the unscheduled DNA synthesis assay in human fibroblasts. Carcinogenicity studies were not conducted because the clinical dosing regimen is a single application. Ivermectin is teratogenic in mice, rats and rabbits at doses at or near maternal toxic doses, which supports a pregnancy category rating of C. The applicant requested a pregnancy category rating of (b) (4) However, no controlled studies in the first trimester were provided. Consultation was obtained from Jeanine Best, MSN, RN, PNP of the Pediatric and Maternal Health Staff,

who found that insufficient data was provided to support a change to pregnancy category (b) (4) and recommended pregnancy category C.

The reader is referred to the comprehensive review by Dr. Jianyong Wang for a full discussion of the nonclinical pharmacology/toxicology data. Dr. Wang and Dr. Barbara Hill did not recommend further nonclinical studies or phase 4 commitments, and recommended an *Approval* action from a pharmacological/toxicological perspective.

5. Clinical Pharmacology/Biopharmaceutics

SKLICE (ivermectin) lotion, 0.5%, is a topical product for the treatment of head lice (b) (4) (b) (4) which is intended to be applied once to dry hair and scalp for ten minutes and then rinsed off with water.

In Study TOP008, the applicant investigated the systemic exposure of ivermectin from one ten-minute application of SKLICE lotion to the hair and scalp of twenty subjects aged 6 months to 3 years with head lice infestation (at least one live louse), thirteen of whom weighed ≤15kg. Blood for pharmacokinetic analysis was obtained at baseline and at 0.5, 1, 6, 24, and 168 hours after application. In one subject, all samples were below the limit of quantitation (BLQ) (<0.05ng/mL). Based on data from the remaining 19 subjects, the mean (±standard deviation) value for C_{max} was 0.241 (±0.233) ng/mL, T_{max} was 15.9 (±10) hr, and AUC_{0-24} was 3.972 (±3.514) ng-h/mL. These values are substantially lower than those seen following oral administration of a single dose of ivermectin 165mcg/kg, albeit by cross-study comparison with TOP001.

In Study TOP001, the applicant investigated the relative bioavailability of ivermectin from an earlier formulation topical ivermectin lotion (b) (4) oral ivermectin, and vehicle lotion. The reader is referred to the review by Dr. Chinmay Shukla for discussion of this study.

The applicant did not conduct a thorough QT/QTc study. Systemic exposure from SKLICE lotion, used per proposed labeling for treatment of pediculosis, is in the subnanomolar range and substantially lower than that seen following oral administration of the tablet formulation. Additionally, ivermectin is not a new molecular entity.

Dr. Shukla found that the applicant met the requirements for approval from a clinical pharmacology perspective, and recommended *Approval* from a clinical pharmacology perspective.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The applicant submitted data from two pivotal trials (Study TOP011 and Study TOP012) to establish the effectiveness of their product applied for 10 minutes in the treatment of head lice infestation. These two studies, identical in design, were randomized, double-blind, placebo-controlled, and parallel-group with two arms. Households were enrolled if one or more member 6 months of age or older was infested with at least 3 live lice; the youngest infested household member with at least 3 live lice was the index subject (primary efficacy cohort) and other infested household members (with at least 1 live louse) were enrolled in the secondary cohort. All subjects in a household received the same treatment. Subjects (or their caregivers) applied the clinical trial material to dry hair and scalp for 10 minutes followed by rinsing on day 1. Subjects were assessed for the presence of live lice on days 2, 8, and 15, and those on whom live lice were identified were provided rescue treatment with an approved OTC pediculocide and considered treatment failures. Treatment success was defined as the absence of live lice. The primary efficacy endpoint was the proportion of index subjects in each treatment group who remain treatment successes (without live lice) on day 15.

The applicant was granted a Special Protocol Assessment, and an Agreement letter was issued on 23 December 2009. Agreements included:

- The general study design
- Definition of the index subject as the youngest family member with 3 live lice
- Dose regimen of a single 10-minute treatment with 0.5% ivermectin cream
- Primary efficacy measure of the absence of live lice in index subjects on day 15
- Primary efficacy endpoint of the proportion within each treatment group of index subjects who are lice-free on day 15
- Primary timepoint of day 15, fourteen days after the last treatment

The results of the primary efficacy endpoint are presented in the following table:

Study	Vehicle	SKLICE	Difference (95% CI)	P-value
	% (n/N)	% (n/N)		
TOP011	16.2% (12/74)	76.1% (54/71)	59.8% (45.5%, 74.2%)	<.001
TOP012	18.9% (14/74)	71.4% (50/70)	52.5% (373%, 67.7%)	<.001

Source: adapted from Statistical Review and Evaluation NDA 202736; Xin Fang, PhD, archived 11.23.2011, p 12.

In Study TOP011 and Study TOP012, SKLICE lotion was superior to vehicle in the proportion of subjects that continued to be lice-free on day 15.

The reader is referred to the biostatistical and clinical reviews by Xin Fang, PhD, and Jane Liedtka, MD, respectively for detailed review of the pivotal trials and additional analyses, including post hoc explorations of the data and sensitivity analyses.

I concur with Drs. Fang and Liedtka that the clinical trial data support a determination of efficacy.

8. Safety

Six hundred and seventy-two subjects with lice infestation were exposed to ivermectin lotion during the development program. Three hundred and seventy-nine of these subjects were exposed to SKLICE lotion in the pivotal trials. Of these subjects, 47 were 6 months to 4 years of age, 179 were 4 years to 12 years of age, and 56 were 12 years to 16 years of age, and 97 were 16 years of age or older.

There were no deaths reported in the development program. Three serious adverse events (SAEs), which resulted in hospitalization, were reported for a single subject in study TOP008: acute gastroenteritis, dehydration, and diaper dermatitis. The SAEs occurred one week after exposure to study drug, resulting in hospitalization 4 days later (11 days after study drug exposure) and resolved without sequelae. The investigator and the clinical reviewer did not consider these SAEs to be related to treatment.

Adverse events were reported more frequently for subjects receiving active than vehicle: 8% versus 6% in the pooled safety population. No adverse events occurred at a frequency of greater than 1%. The most common adverse events occurring at a frequency of <1% in subjects treated with active include conjunctivitis, ocular hyperemia, eye irritation, dandruff, dry skin, and skin burning sensation. Active assessment for ocular and skin irritation did not reveal a safety signal.

Laboratory assessment for white blood cell count was performed in 30 subjects aged 6months to four years in an open-label PK study (TOP008). No significant trend was identified.

A special safety concern is the risk of ingestion-type medication errors. The drug product is packaged in a 4 ounce tube that contains approximately 585mg of ivermectin. Although intended as a single-use product, patients or caregivers may retain the unused portion to retreat if failure or reinfestation occurs, or because they are familiar with a two-application dose regimen from the use of other pediculocides. The container does not have a child-resistant cap. Professional and patient labeling contain instructions to discard unused portions. The risk of accidental ingestion would be reduced with the implementation of a child-resistant cap. The applicant committed to evaluate options for a child-resistant container closure and provide a timeline for implementation of the proposed modification to their packaging by August 2012.

The reader is referred to the clinical review by Dr. Jane Liedtka for a full discussion of the safety database.

9. Advisory Committee Meeting

Not applicable, as no Advisory Committee meeting was held for this application because it did not raise controversial issues that would benefit from outside discussion.

10. Pediatrics

The applicant conducted their pivotal trials and the systemic exposure study 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 not feasible and would be unsafe. Consultation was obtained from the Pediatric and Maternal Health Staff, who concurred with a partial waiver below six months of age and recommended that this be based on the criterion that evidence strongly suggests that the drug would be unsafe in children of that age due to the risk for neurotoxicity as a result of potential immaturity in expression of p-glycoprotein and an increase in the permeability of the blood-brain barrier. Because the waiver is based on a safety concern, this concern is incorporated into labeling. In addition, there is an increased risk of systemic absorption in children less than six months of age because of the high ratio of skin surface are to body mass and the potential for an immature skin barrier, and this is also conveyed in labeling.

The pediatric safety database included 282 subjects with head lice infestation who were exposured to SKLICE lotion: 47 subjects aged 6 months to 4 years, 179 aged 4 years to 12 years, and 56 aged 12 years to 16 years. Thirty of these subjects aged 6 months to 4 years of age underwent laboratory assessment, which did not identify a safety signal. In light of the low systemic exposure relative to oral ivermectin and the extensive postmarketing safety experience with the oral formulation, the Pediatric and Maternal Health Staff found the safety database adequate to make a safety determination, including in subjects 6 months to 2 years of age.

The reader is referred to the consultative review of Dr. Elizabeth Durmowicz for a full discussion of pediatric issues.

11. Other Relevant Regulatory Issues

DSI audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted.

12. Labeling

Dr. Manizheh Siahpoushan of Division of Medication Error Prevention and Analysis found the proposed proprietary name, Sklice, to be acceptable.

All components of labeling were reviewed. Labeling negotiations with the applicant are ongoing at the time of close of this review.

The primary outstanding labeling issue is the indication for the product. The applicant proposed that their product be indicated for, (b) (4)

I recommend that their product be indicated for "the topical treatment of head lice infestation in patients 6 months of age and older" because this wording i) complies with the physicians labeling rule, ii) conforms to accepted medical terminology, iii) is consistent with labeling precedent, and iv) is supported by the applicant's submission. The labeling regulations, 21CFR201.57(c) state that the Indications section of labeling must state that a product is indicated for the treatment of a recognized disease or condition. (b) (4) "head lice infestation" is the recognized disease or condition. Prescription products recently approved for this indication use the terminology, "head lice infestation" in their indication statement in approved labeling. The primary inclusion criterion for enrollment in pivotal trials for this product was "active head lice infestation." (b) (4) (b) (4) (b) (4) The applicant's proposed wording, (b) (4) is misleading (b) (4) (b) (4). For these reasons, I recommend that product labeling state that SKLICE lotion is indicated for the topical treatment of head lice infestation.

Patient labeling was proposed and would be appropriate for this indication.

13. Recommendations/Risk Benefit Assessment

Recommended regulatory action: *Approval*

I concur with the recommendations of the multi-disciplinary review team regarding approval of NDA 202736 SKLICE (ivermectin) lotion, 0.5% for the topical treatment of head lice infestation, pending satisfactory final facilities inspection report and resolution of labeling negotiations.

Risk-benefit assessment: The applicant established the efficacy and safety of SKLICE lotion in the treatment of head lice infestation in patients 6 months of age and older in two adequate and well-controlled trials, and provided sufficient information in their application to support product labeling. The robust efficacy of the product justifies the modest risks, the most serious of which appears to be the risk of ingestion-type medication errors.

Recommended postmarketing Risk Evaluation and Management 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 recommended.

Recommended postmarketing requirements (PMR) and commitments (PMC):

No PMRs are recommended.

The applicant has agreed to a PMC to evaluate child-resistant container closures and provide a timeline for implementation of the proposed modification of the current packaging by August 2012.

Recommended comments to applicant: none

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/s/

JILL A LINDSTROM
02/02/2012