CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202736Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	February 2nd, 2012
From	Susan J. Walker, M.D., F.A.A.D
Subject	Division Director Summary Review
NDA #	202736
Applicant Name	Topaz Pharmaceuticals
Date of Submission	April 7th, 2011
PDUFA Goal Date	February 7th, 2012
Proprietary Name / Established (USAN) Name	Sklice/Ivermectin
Dosage Forms / Strength	Lotion/ 0.5%
Proposed Indication(s)	Treatment of head lice infestation
Action/Recommended Action for NME:	***Approval***

Material Reviewed/Consulted OND Action Package, including:	**Reviewers**
Cross Discipline Team Leader	Jill Lindstrom
Medical Officer Review	Liedtka, Lindstrom
Statistical Review	Fang, Wilson
Pharmacology Toxicology Review	Wang, Hill
CMC Review	David, Strasinger, Rhee
CMC Micro	McVey, Langille
Clinical Pharmacology Review	Shukla, Tran
PMHS	Best, Feibus, Durmowicz, Sachs, Mathis
DMPP	Ford, Fuller, Griffiths
OPDP	Pannholzer, Patel
DSI	Blay, Leibenhaut,Purohit-Sheth
OSE/DMEPA	Siahpoushan, Oleszczuk, Holquist
Project Manager	Williams, Gould

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
PMHS-Pediatric and Maternal Health Staff
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Signatory Authority Review

1. Introduction

This application provides for the approval of topical ivermectin lotion, to be used for the topical treatment of head lice infestation. The development program for this product included meetings and agreements with the agency at major milestones. I am in agreement with the recommendations of the review team for approval of this application. My review will summarize the major areas of the submission and documents my concurrence with the review team's recommendation for approval

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, 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 drug products and also mechanical measures such as combing or shaving of the scalp. 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, and the mature blood-brain barrier is relatively impermeable to ivermectin.

3. CMC/Device

The applicant has provided sufficient information to assure the identity, strength, purity and quality of the drug product. Site inspections were acceptable, and the Office of Compliance has issued an "acceptable" recommendation for the facilities involved in the application. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer, Dr Wang, reviewed two *in vitro* studies evaluating the ovicidal activity of ivermectin topical formulations. Treatment of eggs with 0.5% ivermectin formulation resulted in no significant difference in hatchability compared to treatment with distilled deionized water or placebo.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

TRADENAME (ivermectin) lotion, 0.5%, is a topical product for the treatment of head lice (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 TRADENAME 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 $\leq$15kg. Blood for pharmacokinetic analysis was obtained at baseline and at 0.5, 1, 6, 24, and 168 hours after application. In one subject, all samples were below the limit of quantitation (BLQ) (<0.05ng/mL). Based on data from the remaining 19 subjects, the mean ($\pm$standard deviation) value for C_{max} was 0.241 ($\pm$0.233) ng/mL, T_{max} was 15.9 ($\pm$10) hr, and AUC_{0-24} was 3.972 ($\pm$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.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

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. 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. Efficacy was determined by comparing the

proportion of index subjects in each treatment group who remained treatment successes (without live lice) on day 15.

Study results demonstrating treatment success on day 15 are presented in the following table:

Study	Vehicle	TRADENAME
	% (n/N)	% (n/N)
TOP011	16.2% (12/74)	76.1% (54/71)
TOP012	18.9% (14/74)	71.4% (50/70)

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

I concur with the review team, including the cross-discipline team leader, medical reviewer, biostatistician and biostatistics team leader 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 TRADENAME 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 in the development program and no adverse events with a frequency greater than 1%. Local adverse events can be adequately described in labeling, alerting physicians and patients to the possibility of ocular events and skin irritation. Patients should avoid application to the ocular area, but inadvertent exposure can be managed.

The drug product is packaged in a 4-oz tube and intended as a single use product. I concur with the review team conclusion that the product would benefit from a child-resistant container, and the applicant has agreed to a post-marketing commitment to address this concern.

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. A total of 282 subjects ages 6 months to 16yrs were

exposed to TRADENAME in studies TOP011 and 012. A waiver for pediatric studies below 6 months of age was granted based upon 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 of expression of p-glycoprotein and a subsequent increase in the permeability of the blood-brain barrier. Because the waiver is based on a safety concern, this concern is incorporated into labeling.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

I concur with the recommendations from the review team regarding product labeling, including physician labeling, carton container labeling, and the patient package insert. The proprietary name "SKLICE" was found to be acceptable by DMEPA.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – This product will be approved.
- Risk Benefit Assessment – The benefits of using TRADENAME as labeled outweigh the associated risks. Risks and benefits for use of the product can be adequately conveyed in labeling.
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies - None
- Recommendation for other Postmarketing Requirements and Commitments:
  The applicant has committed to an evaluation of options for a child-resistant container closure system for their product, to include proposing a modification to the approved packaging.

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

/s/

SUSAN J WALKER
02/06/2012