

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202736Orig1s000

PHARMACOLOGY REVIEW(S)

Memorandum

To: NDA 202736
From: Jianyong Wang, Ph.D., Pharmacology/Toxicology Reviewer
Through: Barbara Hill, Ph.D., Pharmacology/Toxicology Supervisor
Re:

Submission date: 04/07/2011
Serial No: SDN 2
Submission type: New NDA
Drug: Sklice (ivermectin) Lotion, 0.5%
Drug class: Pediculicide
Indication: Head lice infestation
Route: Topical
Sponsor: Topaz Pharmaceutical Inc., Horsham, PA

Introduction:

The nonclinical review for this NDA has been entered into DARRTS on 11/16/2001. This NDA is approvable from a pharmacology/toxicology perspective, provided that the recommended changes in the label are incorporated into the SKLICE Lotion label (refer to the previous review).

Two *in vitro* studies that were conducted to evaluate the ovicidal activity of ivermectin formulations and the feeding behavior of 1st instars hatched from eggs treated with ivermectin formulations were submitted to the clinical study section of the NDA. The two studies are reviewed in this memorandum.

Review of study reports:

Study #1

Study title: Ovicidal response of the human head louse, *pediculus humanus capitis*, eggs to ivermectin pediculicide formulations using the hair tuft bioassay

Study no.: None
Study report location: SDN 2
Conducting laboratory and location:  (b) (4)
Date of study initiation: Unknown, report date 10/12/2007
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: Ivermectin formulations, 0.5%, lot# unknown
Formulation: Not provided in this report

Methods:

The ovicidal activity of ivermectin in various formulations on human head lice eggs was evaluated in this study.

Eggs from permethrin-resistant lice (SF-HL strain) deposited on human hair tufts were treated with and without ivermectin in various formulations. Treatments included a 0.5% ivermectin formulation and placebo (provided by Topaz Pharmaceuticals), 0.5% ivermectin in dimethyl sulfoxide (DMSO)/distilled deionized water (ddw) (4:1, v:v), DMSO:DDW (4:1), and DDW. Eggs were collected from feeding cups containing 30 male and 30 female adult lice and were divided into three groups: Group 1 (0-2 day old eggs), Group 2 (3-5 day old eggs), and Group 3 (6-8 day old eggs). The day that adults were placed into feeding cups was designated Day 0. Group 1 was treated on Day 2; Group 2 was treated on Day 5; and Group 3 was treated on Day 8. Tufts with ~60 attached eggs were treated by gently rubbing the tufts into treatment. Treated tufts were placed in a glass dish for a 10 min exposure period at room temperature. At the end of the exposure period, each treated tuft with attached eggs was sequentially washed in three separate ddw baths for 40 sec per wash and dried on filter paper for 5 min at room temperature. Dried tufts with treated eggs were placed into Petri dishes and incubated at 32°C, 70-80% relative humidity. Egg viability was recorded daily. The number of lice that hatched from eggs was recorded and used to determine the percent hatchability of eggs. Undeveloped eggs and stillborn lice were recorded as dead.

Hatched lice were placed onto new hair tufts that had been treated and maintained as the treated hair tufts with eggs and moved to a feeding cup maintained on an *in vitro* rearing system. Survivorship through larval development and adulthood was determined daily.

An additional experiment was performed to assess the possible mortality of hatched lice from residual ivermectin left on the treated hair tufts. Eggs were treated with ivermectin formulation as described above but then removed from the treated hair tuft after drying by clipping the hair strand directly above and below the egg casing. The removed eggs were placed onto untreated hair tufts. The hatchability and survivorship was evaluated in the same manner described above.

Results:

The hatchability, feeding, and survivorship are shown in the copied table below. Treatment of eggs with 0.5% ivermectin formulation resulted in no significant difference in hatchability compared to treatment with ddw or placebo in any of the three aged groups of eggs. The number of 1st instars (hatched lice) that took a blood meal from eggs treated with 0.5% ivermectin formulation was significantly decreased compared to the negative control. All hatched lice treated with 0.5% ivermectin formulation died as 1st instars within 48 hrs, including those hatched lice that fed. Transfer of eggs from treated hair tufts to untreated new tufts resulted no significant difference in hatchability, feeding, or survivorship.

Table 1: Mean percent hatchability, feeding and survivorship to adult (\pm S. D.) of permethrin-resistant human head louse eggs treated at three different egg developmental stages (n = 180).

Treatment	Egg Developmental Stage (Days)								
	0-2			3-5			6-8		
	% Hatch	% Fed	% Adults	% Hatch	% Fed	% Adults	% Hatch	% Fed	% Adults
0.5% Formulated Ivermectin	77.8 \pm 9.6	3.3 \pm 2.7 ^b	0.0 \pm 0.0 ^b	66.7 \pm 7.2	4.4 \pm 1.6 ^b	0.0 \pm 0.0 ^b	75.6 \pm 8.3	5.6 \pm 4.2 ^b	0.0 \pm 0.0 ^b
0.5% Formulated Ivermectin with transfer to untreated tufts	71.5 \pm 9.9	4.4 \pm 4.2 ^b	0.0 \pm 0.0 ^b	70.6 \pm 9.7	2.2 \pm 1.6 ^b	0.0 \pm 0.0 ^b	64.5 \pm 8.9	4.4 \pm 1.6 ^b	0.0 \pm 0.0 ^b
0.5% Unformulated ivermectin ^a	64.8 \pm 7.3	6.8 \pm 3.6 ^b	0.0 \pm 0.0 ^b	67.8 \pm 4.2	5.6 \pm 1.6 ^b	0.0 \pm 0.0 ^b	78.3 \pm 3.6	7.8 \pm 4.2 ^b	0.0 \pm 0.0 ^b
Placebo (sans ivermectin)	80.6 \pm 4.4	67.8 \pm 15.0	38.9 \pm 5.7	82.2 \pm 4.2	67.8 \pm 3.2	40.0 \pm 2.3	80.0 \pm 7.2	76.7 \pm 5.4	42.2 \pm 5.7
DDW	72.2 \pm 5.7	61.7 \pm 14.7	42.2 \pm 11.3	75.6 \pm 9.6	70.0 \pm 5.5	43.3 \pm 5.4	77.8 \pm 4.2	75.5 \pm 5.7	48.9 \pm 8.3
DMSO:DDW	71.1 \pm 9.1	59.5 \pm 12.6	44.4 \pm 10.3	72.6 \pm 9.1	69.3 \pm 7.9	54.5 \pm 8.8	69.3 \pm 7.9	66.3 \pm 7.4	42.2 \pm 8.7

^a Non-formulated ivermectin was dissolved in DMSO: ddw (4:1).

^b Means were significantly different when compared to means of eggs treated with distilled, deionized water using student's t-test

Reviewer's comments: The study showed that 0.5% ivermectin formulation has no ovicidal effects on human head lice eggs. The treatment with 0.5% ivermectin formulation did not significantly affect the hatchability of eggs. However, all the hatched larvae died within 48 hrs. The mortality of hatched larvae may be due to the contact with residue ivermectin on the outside of the eggs during emergence.

Study #2

Study title: Blood-feeding behavior of human head louse 1st instars that hatched from eggs treated with ivermectin using the hair tuft bioassay

Study no.: None

Study report location: SDN 2

Conducting laboratory and location:

(b) (4)

Date of study initiation: Unknown, report date 07/21/2009

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: Ivermectin formulations, 0.5%, lot# unknown

Formulation/Vehicle: Not provided in this report

Methods:

The mortality and feeding behavior of human head louse instars that hatched from eggs treated with ivermectin formulations were evaluated in this study.

Three groups of aged eggs (0-2, 3-5 and 6-8 days) from the permethrin(kdr)-resistant SF-HL strain, oviposited on human hair tufts, were exposed for a 10-minute period either to a placebo solution, to a series of concentrations of ivermectin serially diluted from a 1% ivermectin formulation (10, 2, 1, 0.2, 0.15, or 0.1 µg/ml), or to the same concentrations of neat ivermectin dissolved in DMSO/ddH₂O. Mortality of the hatched instars was observed up to Day 5 after hatching (maximum time for 1st instars to develop into 2nd instars). Blood meals were prepared by mixing a 1 µl aliquot of diluted [³H] inulin solution with 1 ml human blood in the feeding units. The total amount of blood consumed by the lice was then estimated using liquid scintillation spectrophotometry of rinses from feeding units and hair tufts (excrement) and from whole body homogenates (internal).

Results:

Instar mortality and impairment of blood feeding increased with ivermectin concentrations and increased with the interval between oviposition and exposure to ivermectin (age of the egg). Ivermectin concentrations ≤ 0.15 µg/ml, whether formulated or neat, were sublethal to lice hatched from eggs aged 0-6 days at the time of exposure. Over the 5 day observation period, at the concentration of 10 µg/ml (formulated or neat), cumulative mortality were > 70% for the instars hatched from eggs of 0-2 days old, and 100% for the instars hatched from eggs of 3-5 days old and 6-8 days old.

At the concentrations tested for effects on feeding (0.2, 0.15, and 0.1 µg/ml), there was no apparent effect for the first 24 hrs, but the treatment subsequently reduced amounts of blood ingested by the 1st instar lice in a dose dependent manner at 48 hr.

Discussion and conclusions:

The *in vitro* studies showed that the treatment of head lice eggs with ivermectin formulations caused impairment of feeding and mortality of hatched instars in a dose related manner. The impairment of feeding of instars was observed at sublethal doses. However, the hatchability of head lice eggs was not significantly affected by the treatment with 0.5% ivermectin formulation. The impairment of feeding and mortality of hatched instars may be due to the contact with residue ivermectin on the outside of the eggs during emergence. The 0.5% ivermectin formulation was not ovicidal, under the study conditions.

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/s/

JIANYONG WANG
02/02/2012

BARBARA A HILL
02/02/2012
I concur

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 202736
Supporting document/s: SDN 2
Applicant's letter date: 04/07/2011
CDER stamp date: 04/07/2011
Product: SKLICE (ivermectin) Lotion, 0.5%
Indication: *Pediculus humanus capitis* (head lice) infestation
Applicant: Topaz Pharmaceutical Inc., Horsham, PA
Review Division: Dermatology and Dental Products
Reviewer: Jianyong Wang, PhD
Supervisor/Team Leader: Barbara Hill, PhD
Division Director: Susan Walker, MD
Project Manager: Dawn Williams

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Ivermectin is a semisynthetic, antiparasitic agent. Ivermectin is derived from avermectins, a class of broad spectrum antiparasitic agents. Compounds of this class bind selectively with high affinity to glutamate-gated chloride ion channels, which occur primarily in invertebrate nerve and muscle cells. The sponsor intends to develop the SKLICE Lotion product (ivermectin, 0.5%) for the treatment of head lice infestation in patients 6 months of age and older.

This is a 505(b)(1) NDA application because the sponsor submitted a right of reference letter for Stromectrol (ivermectin) tablets (NDA 50742) which allows the Agency to use the nonclinical data available for Stromectrol tablets to support the safety of this drug product.

1.2 Brief Discussion of Nonclinical Findings

Through an *in vitro* dose ranging study the sponsor selected the use of 0.5% lotion with a treatment duration of 10 min for clinical studies. It appears that the head lice mortality rate plateaus at the concentration of 0.5% lotion.

In single dose oral toxicity studies, the signs of toxicity were: ptosis, bradypnea, ataxia, tremors, and loss of the righting reflex (in rodents); mydriasis, ataxia, and tremors (in dogs); emesis, mydriasis, decreased activity and/or sedation (in monkeys).

In repeat dose oral toxicity studies, enlarged spleens with extramedullary hematopoiesis was noted in rats; salivation, mydriasis, anorexia, dehydration, tremors, and ataxia were noted in dogs; no significant toxicities were noted in a study in immature monkeys or in a study in neonatal monkeys. In a 2-week dermal toxicity study in minipigs, no treatment-related dermal or systemic toxicity was noted at topical doses up to 13 mg/kg/day (4% cream, which is the maximum feasible concentration).

Ivermectin appears to be neurotoxic at high oral doses, indicated by signs of mydriasis, tremors, and ataxia, presumably through an effect on GABA neurons. Ivermectin is not genotoxic in the Ames test, mouse lymphoma assay, or the unscheduled DNA synthesis assay.

Ivermectin is teratogenic in mice, rats, and rabbits. Cleft palate, wavy ribs, and clubbed forepaws were seen in these studies. The teratogenic effects were found at or near oral doses that produced maternal toxicity.

The 0.5% ivermectin lotion is a mild irritant to rabbit skin and rabbit eyes. It also induces dermal sensitization in guinea pigs.

The toxicity profile of ivermectin has been well characterized. Per the review for NDA 50742, at the minimum toxic dose of 2 mg/kg in monkeys, the C_{max} was 5.5 times higher than that in humans treated with Stromectol. In a maximum clinical use PK study with SKLICE Lotion, the exposure based on C_{max} and AUC_{0-24} was less than 1.5% of the levels that occur following oral administration of Stromectol.

There is no significant safety concern for systemic toxicity after the use of SKLICE Lotion product due to limited systemic exposure to ivermectin. It is recommended that the animal multiples of human exposure not be provided in the drug label due to the limited systemic exposure. There is also no significant safety concern for dermal toxicity after the use of SKLICE Lotion, based on the result of the dermal minipig study.

This NDA is approvable from a pharmacology/toxicology perspective.

1.3 Recommendations

1.3.1 Approvability

NDA 202736 for SKLICE Lotion (ivermectin, 0.5%) is approvable from a pharmacological/toxicological perspective, provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the SKLICE Lotion label.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the SKLICE Lotion label reproduced below. The pharmacologic class designation for ivermectin for the treatment of head lice is pediculicide. The wording describing human data under Section 8.1 is provided by the clinical reviewer.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

SKLICE Topical Lotion is ^{(b) (4)} a pediculicide indicated for the topical treatment of head lice and ^{(b) (4)} their ova in patients 6 months of age and older.

8.1 Pregnancy

Pregnancy Category ^{(b) (4)} C

There are no adequate and well-controlled studies with SKLICE Topical Lotion in pregnant women. SKLICE Topical Lotion should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No comparisons of animal exposure with human exposure are provided in this label due to the low systemic exposure noted in the clinical pharmacokinetic study [see *Clinical Pharmacology* (12.3)].

Human Data

There are published reports of ivermectin use during human pregnancy. In an open label study, 397 women in their second trimester of pregnancy were treated with ivermectin and albendazole at the labeled dose rate for soil-transmitted helminths and compared with a pregnant, non-treated population. No differences in pregnancy outcomes were observed between treated and untreated populations.

Animal Data

Systemic embryofetal development studies were conducted in mice, rats and rabbits. Oral doses of 0.1, 0.2, 0.4, 0.8, and 1.6 mg/kg/day ivermectin were administered during the period of organogenesis (gestational days 6–15) to pregnant female mice. Maternal death occurred at 0.4 mg/kg/day and above. Cleft palate occurred in the fetuses from the 0.4, 0.8, and 1.6 mg/kg/day groups. Exencephaly was seen in the fetuses from the 0.8 mg/kg group. Oral doses of 2.5, 5, and 10 mg/kg/day ivermectin were administered during the period of organogenesis (gestational days 6–17) to pregnant female rats. Maternal death and pre-implantation loss occurred at 10 mg/kg/day. Cleft palate and wavy ribs were seen in fetuses from the 10 mg/kg/day group. Oral doses of 1.5, 3, and 6 mg/kg/day ivermectin were administered during the period of organogenesis (gestational days 6–18) to pregnant female rabbits. Maternal toxicity and abortion occurred at 6 mg/kg/day. Cleft palate and clubbed forepaws occurred in the fetuses from the 3 and 6 mg/kg groups. These teratogenic effects were found only at or near doses that were maternally toxic to the pregnant female. Therefore, ivermectin does not appear to be selectively fetotoxic to the developing fetus.

(b) (4)

12.1 Mechanism of Action

Ivermectin, (b) (4)-a member of the avermectin class, (b) (4) causes (b) (4)-death of parasites primarily through binding selectively and with high affinity to glutamate-gated chloride channels, (b) (4) which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA). The selective activity of compounds of this class is attributable to the fact that some mammals do not have glutamate-gated chloride channels and that the avermectins have a low affinity for mammalian ligand-gated chloride channels. In addition, ivermectin does not readily cross the blood-brain barrier in humans. (b) (4)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of SKLICE Topical Lotion or ivermectin.

Ivermectin was not genotoxic *in vitro* in the Ames (b) (4) est, the mouse lymphoma assay, or the unscheduled DNA synthesis assay in human fibroblasts.

Ivermectin had no adverse effects on fertility in rats at repeated oral doses of up to 3.6 mg/kg/day.

2 Drug Information

2.1 Drug

CAS Registry Number:

Ivermectin 70288-86-7; Component H₂B_{1a} 70161-11-4; Component H₂B_{1b} 70209-81-3

Generic Name: Ivermectin lotion, 0.5%

Code Name: KB21 and KB100

Chemical Name:

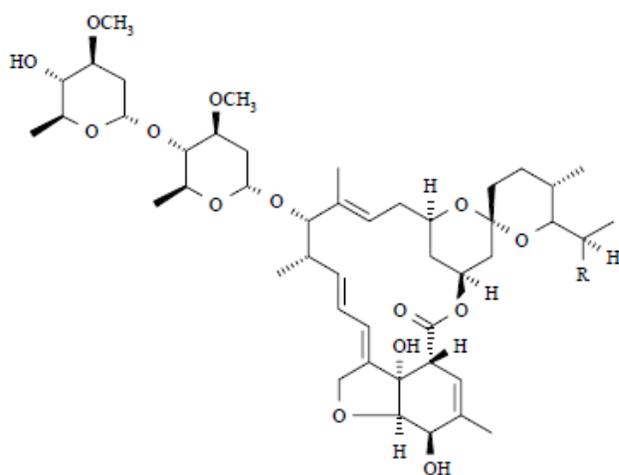
Ivermectin is a mixture containing at least 90% 5-O-demethyl-22,23 dihydroivermectin A_{1a} and less than 10% 5-O-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)ivermectin A_{1a}, generally referred to as 22,23-dehydroivermectin B_{1a} and B_{1b}, or H₂B_{1a} and H₂B_{1b}, respectively.

Molecular Formula/Molecular Weight:

Component H₂B_{1a}: C₄₈H₇₄O₁₄ / 875.10

Component H₂B_{1b}: C₄₇H₇₂O₁₄ / 861.07

Structure or Biochemical Description:



Component H₂B_{1a}: R = CH₂CH₃; Component H₂B_{1b}: R = CH₃

Pharmacologic Class: pediculicide (Note: Although “antiparasitic” was used previously as an established pharmacologic class for ivermectin, for the SKLICE Lotion product, “pediculicide” is recommended by the clinical reviewer as it is considered more clinically meaningful.)

2.2 Relevant INDs, NDAs, BLAs and DMFs

(b) (4)	(b) (4)
IND 57420	Stromectol tablet (ivermectin), head lice infestation, DDDP (b) (4)
IND 73134	Ivermectin cream 0.5%, head lice infestation, DDDP (b) (4)
NDA 50742	Stromectol (mectizan) tablet (ivermectin), strongyloidiasis and onchocerciasis, approved on 11/22/1996

2.3 Drug Formulation

The composition of SKLICE Lotion is listed in the following table.

Component	Quality Standard	Function	%w/w
Ivermectin	USP	Drug Substance	0.5
Purified Water	USP	(b) (4)	
Olive Oil	NF		
Crodalan AWS	In house		
Oleyl alcohol	NF		
Lanolin alcohol	NF		
Cyclomethicone	NF		
Shea butter	In house		
Sorbitan tristearate	In house		
Methylparaben	NF		
Propylparaben	NF		
Citric Acid	USP		
Sodium Citrate	USP		

Crodalan AWS is composed of (b) (4)

The sponsor has made minor changes to the original formulation to (b) (4) (b) (4) of the drug product (changes shown in bold in the table below). The dermal toxicity study (in minipigs) was conducted with the original formulation. The changes are not considered significant regarding the toxicity profile of the drug product. Therefore, the conducted dermal minipig study is acceptable to support the marketing of the final clinical formulation.

Note: It is determined by the chemistry reviewer that “lotion” is more appropriate than “cream” to describe the clinical formulation. “Cream” has been used in the nonclinical study reports and previous reviews under IND 73134. Changing the name of the ivermectin formulation from “cream” to “lotion” does not affect the composition of the drug product.

Ingredient	Original clinical formulation (% w/w)	Final clinical formulation (% w/w)
Ivermectin	0.5	0.5
Crodalan, AWS	(b) (4)	(b) (4)
Oleyl alcohol, NF		
Lanolin alcohol, NF		
Cyclomethicone, NF		
Shea butter		
Sorbitan tristearate		
Methylparaben, NF		
Propylparaben, NF		
Citric acid		
Sodium citrate		
Purified water, USP		
Olive oil, NF		
Total		100.00

2.4 Comments on Novel Excipients

Three excipients, shea butter, sorbitan tristearate and (b) (4) crodalan AWS) are not listed in the CDER inactive ingredient database. The sponsor provided a toxicological assessment of the three novel excipients in the submission.

1. Shea butter (b) (4)

Shea butter is (b) (4) often used in relatively large amounts (concentrations of 60% have been reported in some leave-on cosmetic products). According to the Voluntary Cosmetic Registration Program, 1950 cosmetic and personal care products containing shea butter were reported to the FDA in 2009. Of those products 1680 are classified as leave-on formulations; 270 are rinse-off formulations. Concentrations of shea butter range between 0.0005 to 30% for rinse-off products and between 0.001 to 60% for leave-on products.

The human safety of shea butter, over many years of use in both cosmetics and foods, is extensive. In animal studies, shea butter was not found to be either an ocular or a dermal irritant or sensitizer. Shea butter was found to be non phototoxic. Shea butter is obtained from processing shea nut oil. Shea nut oil is generally recognized as safe (GRAS) (21CFR 184.1702) as a direct human food ingredient. Shea butter is a formulation excipient in the FDA-approved, non-steroidal product Atopiclair[®] cream (Graceway Pharmaceuticals LLC, 2009) which received marketing authorization as a medical device for the relief of symptoms of atopic dermatitis and contact dermatitis.

2. Sorbitan tristearate (b) (4)

Sorbitan tristearate is used [REDACTED] (b) (4) in topical cosmetic formulations. It is also allowed as an indirect food additive (21CFR 178.3400) by the FDA and by the Joint FAO/WHO (Food and Agriculture Organization/World Health Organization) Expert Committee on Food Additives (JECFA) with a European food additive listing number of E492. In cosmetic products, concentrations of sorbitan tristearate typically range between 0.1% and 5% (up to 10%).

Sorbitan tristearate has been found to be non-irritating when tested in animals and in humans. In Draize-type irritation testing, a 30% sorbitan tristearate solution produced no irritation 72 hr after being applied to rabbit skin under occlusion for 24 hr. Animal studies indicate that sorbitan tristearate is not an eye irritant. In ocular irritation tests in rabbits, 30% and 40% concentration of sorbitan tristearate did not show any ocular irritation.

A single oral dose of sorbitan tristearate as a 30% w/v suspension in 0.5% carboxymethylcellulose was given to 20 fasted rats at 15.9 g/kg, the maximum feasible oral dose. No deaths or signs of toxicity were observed during the 14-day observation period. A 2-year chronic feeding study was conducted with 5% sorbitan tristearate in 30 male rats. There was no alteration in growth pattern or survival of the test rats as compared to the controls, nor were any abnormalities attributed to the experimental diet.

(b) (4)

The toxicity profile of sorbitan tristearate and [REDACTED] (b) (4) was discussed previously and the proposed concentrations for the two novel excipients are considered acceptable. Shea butter [REDACTED] (b) (4) does not cause a safety concern.

In addition, the sponsor has conducted nonclinical a dermal irritation study, an ocular irritation study and a 2 week dermal minipig toxicology study with an ivermectin cream formulation that contained the three novel excipients. The data from these studies

provide additional data to support the safety of these three novel excipients contained in SKLICE Lotion. All the three novel excipients are acceptable at the proposed concentrations.

2.5 Comments on Impurities/Degradants of Concern

None.

2.6 Proposed Clinical Population and Dosing Regimen

Clinical population: Patients with head lice infestation, 6 months of age and older

Dosing regimen: Single application. SKLICE Lotion (up to 1 tube, (b) (4) which contains (b) (4) ivermectin) is to be applied to dry hair and left on the hair and scalp for 10 min, then rinsed off with water.

2.7 Regulatory Background

Initially the sponsor intended to develop the 0.5% ivermectin lotion as a 505(b)(2) NDA application by establishing a clinical bridge to the systemic safety data available for ivermectin tablets (Stromectol[®], approved under NDA 50742). A pre-IND meeting was conducted with the sponsor on 07/24/2006. An End-of-Phase 2 meeting was conducted with the sponsor on 08/12/2009. In the NDA submission the sponsor provided a right of reference letter from Merck, which authorizes permission to reference the nonclinical toxicology and clinical safety data contained in NDA 50742. Therefore, this NDA is a 505(b)(1) application.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology studies:

1. Mortality response of the Human head louse, *Pediculus humanus capitis*, to ivermectin pediculicide formulations using the hair tuft bioassay
2. *In vitro* dose ranging study of five topical ivermectin (TPZ-0434) formulations to evaluate the effectiveness against head lice (*Pediculus humanus capitis*) (Study# TNC-09001)

General Toxicology Studies:

1. Pilot report: Toxicokinetics of ivermectin in miniature swine (Study# S06514)
2. 2-week repeat dose dermal toxicity study of ivermectin in minipigs followed by a 1-week recovery period (Study# S06506)

Special toxicology studies:

1. Primary dermal irritation in rabbits, primary ocular irritation in rabbits and guinea pig maximization test (Study# T07-0450)

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Nonclinical review, NDA 50742, by Dr. Kenneth Seethaler, 07/30/1996

Nonclinical review, IND 73134, by Dr. Barbara Hill, 05/30/2007

Memorandum, IND 73134, by Dr. Barbara Hill, 02/25/2008

Memorandum, IND 73134, by this reviewer, 08/17/2009

4 Pharmacology

4.1 Primary Pharmacology

Ivermectin is a semisynthetic, anti-parasitic agent derived from avermectins, a class of broad-spectrum anti-parasitic agents. Ivermectin has broad activity against nematodes and arthropods including virtually all insects.

Compounds of this class bind selectively with high affinity to glutamate-gated chloride ion channels, which occur primarily in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA). The selective activity of compounds of this class is attributable to the fact that some mammals do not have glutamate-gated chloride channels and that the avermectins have a low affinity for mammalian ligand-gated chloride channels. In addition, ivermectin does not readily cross the blood-brain barrier in humans.

A nonclinical *in vitro* assay was conducted to evaluate the efficacy of the ivermectin cream clinical formulation. Permethrin-resistant head lice were treated with 0.25%, 0.5% and 1% ivermectin cream for 10 min. In addition, permethrin-resistant head lice were treated with 0.5% ivermectin cream for 3 and 5 min. The bioassay used for this study was an *in vitro* lice rearing system and a hair tuft bioassay model developed at the (b) (4). Thirty lice were individually placed onto hair tufts and treated with ivermectin cream. Then each hair tuft was rinsed 3 times (5 sec each) and air dried for 5 min. Mortality was then assessed at 10 min intervals until >90% mortality was achieved. Mortality of lice when viewed under a dissecting microscope was defined as cessation of all leg movement and the inability of the lice to right themselves when inverted. Ovicidal activity was not assessed in this study.

The median time to 95% mortality (LDT_{95}) values for the 0.25%, 0.5%, and 1% ivermectin cream were 209, 130 and 88 min, respectively. A dose-dependent decrease in mortality times (LDT_{95}) was noted in this study. The LDT_{95} values after 3, 5 or 10 min exposures to 0.5% ivermectin cream were 426, 197 and 130 min, respectively. A time-dependent decrease in LDT_{95} was noted in this study. The sponsor selected use of 0.5% cream with a treatment duration of 10 min for clinical studies based on the results of this study.

In an *in vitro* dose ranging study, lice of all stages were removed from naturally infested volunteers and placed in petri dishes where they gathered in hair tufts. Then they were exposed to five concentrations of ivermectin cream (0.05%, 0.15%, 0.25%, 0.5%, and 1.0%), vehicle control, or water control for 10 min followed by a 12 hr observation period (observation time points: every 15 min for first 5 hr then hourly up to 12 hr post-rinsing).

Head lice mortality produced by ivermectin cream was clearly dose-dependent. Similar low head lice mortality rates were observed for water, vehicle, and 0.05% ivermectin at each time point. Head lice mortality from exposure to 0.25% and 0.15% ivermectin did not differ significantly from the vehicle until after 5 hr and 10 hr, respectively. Both the 0.5% and 1.0% ivermectin produced higher mortality rates than the vehicle from 2 hr to 12 hr, with >90% mortality produced by the 0.5% cream by 7 hr post-rinsing. The 0.5% concentration produced significantly greater mortality than did the 0.25% concentration from 3 through 7 hr post-rinsing (66.0% and 35.5%, respectively). It appeared that the head lice mortality rate plateaus at the concentration of 0.5% for ivermectin cream.

4.2 Secondary Pharmacology

N/A

4.3 Safety Pharmacology

None. Safety pharmacology studies are not needed to support the development of SKLICE Lotion due to limited systemic exposure to ivermectin after a single 10 min topical application.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Oral bioavailability of ivermectin is low and ivermectin is slowly eliminated (half-lives ranged from 12–18 hr). The primary route of excretion is in the feces. The majority of radioactivity associated with ivermectin after oral administration to rats is excreted within 48 hr. The fraction of ivermectin that was metabolized was higher after oral administration indicating a first-pass effect. Demethylation and hydroxylation appeared to be the main metabolic reactions and no significant gender differences in metabolism were noted in rats. Ivermectin was widely distributed in tissues and no blood brain barrier passage was noted after either oral or intravenous administration in rats.

Ivermectin was highly bound to plasma proteins (99.9%) in mouse, rat, rabbit, dog, minipig and human.

5.2 Toxicokinetics

Included in toxicology studies.

6 General Toxicology

6.1 Single-Dose Toxicity

The median lethal doses (LD₅₀s) of ivermectin were reported as follows:

11.6 mg/kg (oral) in male mice
24.6-87.2 mg/kg (oral) in female mice
42.8-52.8 mg/kg (oral) in male rats
44.3-52.8 mg/kg (oral) in female rats
2.3 mg/kg (oral) in infant rats (1-2 day old pups)
406 mg/kg (dermal) in rabbits (both sexes)

The signs of toxicity observed in rodents were ptosis, bradypnea, ataxia, tremors, and loss of the righting reflex. A study was conducted in dogs using single oral doses of 5-80 mg/kg. Mydriasis, ataxia, and tremors occurred at 10 mg/kg. Two of the four dogs dosed at 80 mg/kg became comatose and died.

In an ascending dose toxicity study in rhesus monkeys (NDA 50742, Study# TT-85-013-0, GLP), ivermectin was administered via gavage in sesame oil to immature monkeys (2/sex/group, 2-3 years old, 2.4-3.2 kg) at single oral doses of 0.2, 0.5, 1, 2, 4, 6, 8, 12, and 24 mg/kg (5 ml/kg), with intervals of 2-3 weeks between doses. Body weights and food consumption were recorded, and the animals were observed for signs of toxicity. Emesis was observed in these animals, with a dose-related incidence at doses of 2 mg/kg and higher. Mydriasis was seen at doses of 6 mg/kg and above. Decreased activity and/or sedation occurred at 24 mg/kg. The minimum toxic dose was 2 mg/kg, at which the peak plasma drug concentration was highest at 24 hr and averaged 110 ng/ml. No postmortem or microscopic observations were reported for this study.

6.2 Repeat-Dose Toxicity

In a 2-week oral toxicity study in immature rhesus monkeys (NDA 50742, study# TT-85-9033, GLP), ivermectin in sesame oil was administered to monkeys (4/sex/group, 13-21 months old, 1.9-3.2 kg) via nasogastric incubation at doses of 0, 0.3, 0.6, or 1.2 mg/kg/day (1 ml/kg), once daily for 14-16 days. Evaluations included clinical observation, body weight, hematology, serum chemistry, ophthalmology, gross pathology, organ weight, and microscopic histopathology. No treatment-related findings were noted in this study.

In a 2-week oral toxicity study in neonatal rhesus monkeys (NDA 50742, study# TT-86-9005, GLP), neonatal rhesus monkeys (5 males and 3 females/group, 7-13 days old, 400-600 g) were maintained on a bottled infant formula in individual incubators in the nursery. Ivermectin in sesame oil was administered via nasogastric incubation, at doses of 0, 0.04, or 0.1 mg/kg/day (1 ml/kg), once daily for 14 days. Evaluations included clinical observation, body weight, food consumption, hematology, serum chemistry, ophthalmology (including pupillary light responses), gross pathology, organ weights, and microscopic histopathology. No treatment-related effects were observed in this study.

A 14-week oral toxicity study was conducted in rats (20/sex/group) at doses of 0, 0.4, 0.8, and 1.6 mg/kg/day (NDA 50742). The animals used in this study were derived from dams that had also been treated with the compound. The no-effect level was 0.4 mg/kg/day. At higher doses, the following gross and microscopic signs of toxicity were observed: enlarged spleens with congestion of the red pulp and extramedullary hematopoiesis, iron-positive pigment in renal tubular epitheliums, hepatocellular vacuolation and pigment in Kupffer cells. Reactive hyperplasia of the bone marrow was seen in the animals with enlarged spleens, suggesting possible intravascular hemolysis.

A 14-week oral toxicity study was conducted in dogs (4/sex/group) at doses of 0, 0.5, 1, and 2 mg/kg/day (NDA 50742). The no-effect level was 0.5 mg/kg/day. The signs seen at higher doses were salivation, mydriasis, anorexia, dehydration, tremors, and ataxia. Some of the animals became recumbent, and 4 of the 8 dogs in the high dose group were sacrificed in poor condition.

Two Hanford minipigs received topical administration of 4% ivermectin cream to 10% of the body surface area (BSA) for 3 days. Test article was applied for 10 min on Day 1, for 4 hr on Day 2 and for 8 hr on Day 3. Test article was removed from the treatment site following the exposure period with gauze soaked with deionized water. The treatment site was unoccluded on Day 1 and covered with a body stockinette on Days 2 and 3. Toxicity parameters assessed in this study included mortality, dermal and clinical signs, food consumption, body weights and gross necropsy. Blood samples were obtained on Days 1, 2 and 3 for toxicokinetic analysis. No treatment related effects were noted in this study. No erythema or edema was noted in Day 1 animals, Day 2 animals and the Day 3 male. Slight erythema was noted in the female animal on Day 3. All plasma samples collected from the male and female minipigs on Days 1, 2 and 3 were below the lower limit of quantitation for ivermectin (LLOQ = 10 ng/ml) in this study.

Topical doses of 0% (vehicle), 0.5%, 1.0% and 4.0% ivermectin cream (0, 1.6, 3.3 and 13 mg/kg/day ivermectin, respectively; dose volume 0.32 ml/kg) were administered to 10% BSA of Hanford minipigs (3/sex/dose) for 1 hr per day for 14 days, followed by a 7-day recovery period. Toxicity parameters assessed in this study included mortality, dermal and clinical signs, body weights, food consumption, ophthalmology, ECG, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology. No treatment related dermal or systemic toxicity was noted in this

study. Therefore, the NOAEL is identified as 4% ivermectin cream (13 mg/kg/day; 455 mg/cm²/day), under the conditions of this study. No systemic exposure to ivermectin was noted on Day 1 and sporadic plasma samples were marginally above LLOQ for ivermectin on Day 14. The 4.0% ivermectin cream is the maximum feasible concentration.

7 Genetic Toxicology

The following genetic toxicology information is contained in the Stromectol label.

“Ivermectin was not genotoxic *in vitro* in the Ames microbial mutagenicity assay of *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 with and without rat liver enzyme activation, the Mouse Lymphoma Cell Line L5178Y (cytotoxicity and mutagenicity) assays, or the unscheduled DNA synthesis assay in human fibroblasts.”

8 Carcinogenicity

No carcinogenicity data are available for ivermectin. Treatment of lice infestation is an acute indication. Carcinogenicity studies are not needed to support the marketing of SKLICE Lotion, at this time.

9 Reproductive and Developmental Toxicology

Several teratology studies were conducted in mice (20-25 dams/group) with ivermectin at oral doses of 0, 0.1, 0.2, 0.4, 0.8, and 1.6 mg/kg/day, administered during gestation Days 6-15 (NDA 50742). Tremors and convulsions were seen in some dams following doses of 0.2 mg/kg/day. Some maternal deaths occurred at doses of 0.4 mg/kg/day and higher. Teratogenic effects were seen at doses of 0.4 mg/kg/day and above. Cleft palate occurred in the fetuses from the 0.4, 0.8, and 1.6 mg/kg/day groups. Exencephaly was seen in the 0.8 mg/kg group.

A teratology study was conducted in rats (25 dams/group) with ivermectin at oral doses of 0, 2.5, 5, and 10 mg/kg/day, administered during gestation Days 6-17 (NDA 50742). There were some maternal deaths, and some pre-implantation loss in the high dose group. Incomplete bone ossification occurred in the 5 and 10 mg/kg/day groups. Cleft palate and “wavy ribs” were seen in the 10 mg/kg group.

A teratology study was conducted in rabbits (16 dams/group) with ivermectin at oral doses of 0, 1.5, 3, and 6 mg/kg/day, administered during gestation Days 6-18 (NDA 50742). In the high dose group, there were losses in maternal body weights, and some abortions. There was also an increase in the number of dead fetuses. Cleft palate and clubbed forepaws occurred in the fetuses from the 3 and 6 mg/kg groups.

Some additional reproduction studies that were conducted in rats (NDA 50742) showed that ivermectin produced adverse effects in neonates (delayed development, increased

pup mortality). These effects occurred at maternal doses of 1.6 mg/kg/day and above. It was also shown that the compound was secreted in the milk of lactating rats.

The following reproductive toxicology information is contained in the Stromectol label.

“Ivermectin had no adverse effects on the fertility in rats in studies at repeated doses of up to 3 times the maximum recommended human dose of 200 mcg/kg (on a mg/m²/day basis).”

“Pregnancy Category C

Ivermectin has been shown to be teratogenic in mice, rats, and rabbits when given in repeated doses of 0.2, 8.1 and 4.5 times the maximum recommended human dose, respectively (on a mg/m²/day basis). Teratogenicity was characterized in the three species tested by cleft palate; clubbed forepaws were additionally observed in rabbits. These developmental effects were found only at or near doses that were maternotoxic to the pregnant female. Therefore, ivermectin does not appear to be selectively fetotoxic to the developing fetus. There are, however, no adequate and well-controlled studies in pregnant women. Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.”

The sponsor proposed a change of pregnancy category (b) (4) (b) (4) for their SKLICE Lotion product, (b) (4)

(b) (4) The CDER maternal health team reviewed the submitted literature and has concluded that SKLICE (ivermectin) Lotion, 0.5%, should be classified as a pregnancy category C at this time as the sponsor did not submit adequate data to classify the drug as a pregnancy category (b) (4) (PMHS review, 07/19/2011).

Because the systemic exposure to ivermectin after the use of SKLICE Lotion is very limited (refer to the clinical pharmacology review), it is recommended that the animal multiples of human exposure not be provided in the drug label.

10 Special Toxicology Studies

The sponsor submitted a UV spectral analysis report to IND 73134 to show the UVB/UVA/Visible light absorbance (290-700 nm) of each ingredient in the clinical ivermectin lotion formulation. Potassium dichromate was used as a positive control. Among all the ingredients, only cyclomethicone and lanolin alcohol showed low absorbance around 290 nm. Because there is generally very low absorbance in the range of 290-700 nm for the drug product, and the SKLICE Lotion will be used in a short duration generally inside the house, phototoxicity is not considered a concern for this drug product from a pharmacology/toxicology perspective.

Primary dermal irritation and ocular irritation studies were conducted with 0.5% ivermectin lotion in rabbits and a dermal sensitization study was conducted with 0.5% ivermectin lotion in guinea pigs. Minimal erythema and very slight edema were noted at

the unabraded and abraded treatment sites at 24 hr post dose. The extent of erythema and edema decreased by the 72 hr time point, but total recovery was not noted over the 72 hr period. The 0.5% ivermectin lotion was considered a mild irritant to intact and abraded rabbit skin after a 24 hr topical application under occlusion. The 0.5% ivermectin lotion was a mild ocular irritant in un-rinsed rabbit eyes (mild to moderate conjunctival redness was noted). The 0.5% ivermectin lotion was classified as a sensitizer in guinea pigs using a maximization test study design (slight edema was noted post challenge).

11 Integrated Summary and Safety Evaluation

Ivermectin binds selectively with high affinity to glutamate-gated chloride ion channels, which occur primarily in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Ivermectin may also interact with other ligand-gated chloride channels, such as GABA channel. Through an *in vitro* dose ranging study the sponsor selected the use of 0.5% cream with a treatment duration of 10 min for clinical studies. In another *in vitro* dose ranging study, concentrations of ivermectin from 0.05% to 1% were tested and it appears that the head lice mortality rate plateaus at the concentration of 0.5% for ivermectin cream.

In single-dose toxicity studies, the signs of toxicity observed in rodents were ptosis, bradypnea, ataxia, tremors, and loss of the righting reflex. In a single oral dose toxicity study in dogs, mydriasis, ataxia, and tremors occurred at 10 mg/kg. In a single ascending oral dose toxicity in immature monkeys, emesis was observed at 2 mg/kg and above; mydriasis was noted at 6 mg/kg and above; decreased activity and/or sedation occurred at 24 mg/kg. 2 mg/kg was considered the LOAEL.

In a 2-week oral toxicity study in immature rhesus monkeys, ivermectin doses of 0, 0.3, 0.6, and 1.2 mg/kg/day were administered once daily for 14-16 days. No treatment-related findings were noted in this study. The NOAEL was the high dose tested, 1.2 mg/kg/day. In a 2-week oral toxicity study in neonatal rhesus monkeys, ivermectin doses of 0, 0.04, and 0.1 mg/kg/day were administered once daily for 14 days. No treatment-related effects were observed in this study. The NOAEL was the high dose tested, 0.1 mg/kg/day.

In a 14-week oral toxicity study in rats, ivermectin doses of 0, 0.4, 0.8, and 1.6 mg/kg/day were tested. The NOAEL was 0.4 mg/kg/day. At higher doses, the following signs of toxicity were observed: enlarged spleens with extramedullary hematopoiesis, iron-positive pigment in renal tubular epitheliums, hepatocellular vacuolation and pigment in Kupffer cells. Reactive hyperplasia of the bone marrow was seen in the animals with enlarged spleens, suggesting possible intravascular hemolysis.

In a 14-week oral toxicity study in dogs, ivermectin doses of 0, 0.5, 1, and 2 mg/kg/day were tested. The NOAEL was 0.5 mg/kg/day. The signs seen at higher doses were salivation, mydriasis, anorexia, dehydration, tremors, and ataxia.

In a 2-week dermal toxicity study in minipigs, ivermectin doses of 0, 1.6, 3.3, and 13 mg/kg/day were applied to 10% BSA, 1 hr per day for 14 days (0%, 0.5%, 1.0%, and 4% cream, dose volume 0.32 ml/kg). No treatment-related dermal or systemic toxicity was noted in this study. The NOAEL was the high dose tested, 13 mg/kg/day (4% cream).

Ivermectin appears to be neurotoxic at high oral doses, indicated by signs of mydriasis, tremors, and ataxia, presumably through an effect on GABA neurons. Ivermectin is not genotoxic in the Ames test, mouse lymphoma assay, or the unscheduled DNA synthesis assay.

Ivermectin is teratogenic in mice, rats, and rabbits. Cleft palate was seen in mice at doses of 0.4 mg/kg/day and above. Cleft palate and wavy ribs were seen in rats at dose of 10 mg/kg/day. Cleft palate and clubbed forepaws were seen in rabbits at doses of 3 mg/kg/day and above. The teratogenic effects were found at or near maternal toxic doses.

The 0.5% ivermectin lotion is a mild irritant to rabbit skin and rabbit eyes. It also induces dermal sensitization in guinea pigs.

The toxicity profile of ivermectin has been well characterized. Per the review for NDA 50742, at the minimum toxic dose of 2 mg/kg in monkeys, the C_{max} was 5.5 times higher than that in humans (110 ng/ml vs. 20 ng/ml). In a maximum clinical use PK study with SKLICE lotion, the exposure based on C_{max} (0.24 ng/ml) and AUC_{0-24} (3.972 ng.h/ml) was less than 1.5% of the levels that occur following oral administration of a single dose of 12 mg Stromectol.

There is no significant safety concern for systemic toxicity after the use of SKLICE Lotion product due to limited systemic exposure to ivermectin. It is also not recommended to provide the animal multiples of human exposure in the drug label due to the limited systemic exposure. There is also no significant safety concern for dermal toxicity after the use of SKLICE Lotion, based on the results of the 2-week dermal minipig study (no toxicity was noted at the dermal dose of 4% cream, which is the maximum feasible concentration).

This NDA is approvable from a pharmacology/toxicology perspective.

12 Appendix/Attachments

None.

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

/s/

JIANYONG WANG
11/16/2011

BARBARA A HILL
11/16/2011
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 202736

Applicant: Topaz Pharmaceuticals Inc.,
Horsham, PA

Stamp Date:
04/07/2011

Drug Name: Sklice
(ivermectin) Cream, 0.5%

NDA Type: Original-505(b)(1)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		This is an electronic CTD submission.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		A right of reference letter is provided that allows the Agency to use the preclinical toxicology data contained in NDA 50742 to support this NDA. Use of a right of reference letter makes this a 505(b)(1) NDA.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		The sponsor made slight changes in the formulation to improve preservative characteristics. Such minor changes are not considered significant regarding toxicity profile and no additional toxicity study is recommended.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		X	The animal multiples of the maximum recommended human dose were copied from the Stromectol label. The multiples should be modified because the human exposure to ivermectin is different for the two drug products.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			It is not applicable to this NDA supplement.
11	Has the applicant addressed any abuse potential issues in the submission?			It is not applicable to this NDA supplement.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			This NDA supplement is not to support a Rx to OTC switch.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. It appears that the animal multiples of the maximum recommended human dose described in Sections 8.1 and 13.1 were copied from the Stromectol label. These multiples should be modified because the human exposure to ivermectin is different when using your drug product and Stromectol tablet.

Jianyong Wang see sign-off date

 Reviewing Pharmacologist Date

Barbara Hill see sign-off date

 Team Leader/Supervisor Date

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

/s/

JIANYONG WANG
05/27/2011

BARBARA A HILL
05/31/2011