CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-129

PHARMACOLOGY REVIEW(S)

Comments on NDA 22-129 benzyl alcohol lotion lice asphyxiator

From A. Jacobs, AD for Pharm/tox
Date March 30, 2009

I have reviewed the pharm/tox review and the supervisory memo.

I agree that there are no outstanding pharm/tox issues.
I agree that category B as a pregnancy category is appropriate.
I agree with the pharm/tox supervisory memo which explains that for nonclinical sections of labeling, that multiples of the clinical exposure at which adverse effects or no adverse effects occurred should not be included because it is impossible to calculate the multiples of exposure. This is because the systemic exposure in humans is so low as not being measurable.

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

/s/

Abby Jacobs
3/30/2009 03:02:32 PM
PHARMACOLOGIST

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-129**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**June 15, 2007**
PRODUCT:	**Lice asphyxiator (benzyl alcohol), 5%**
INTENDED CLINICAL POPULATION:	***Pediculus humanus capitis* (head lice) of the scalp hair**
SPONSOR:	**Summer Laboratories, Inc.**
DOCUMENTS REVIEWED:	**Electronic CTD NDA submission**
REVIEW DIVISION:	**Division of Dermatology and Dental Products (HFD-540)**
PHARM/TOX REVIEWER:	**Barbara Hill, Ph.D.**
PHARM/TOX SUPERVISOR:	**Paul Brown, Ph.D.**
DIVISION DIRECTOR:	**Susan Walker, M.D.**
PROJECT MANAGER:	**Melinda Bauerlien**

Date of review submission to Division File System (DFS): 2-12-08

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability – The lice asphyxiator drug product NDA is approvable from a pharmacological/toxicological perspective.

B. Recommendation for nonclinical studies – None

C. Recommendations on labeling – Recommended wording for the nonclinical portions of the label are provided in the "Suggested Labeling" section located at the end of this review.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings – Results from 13 week repeat dose oral rat and mouse toxicology studies conducted by the National Toxicology Program suggest that high doses of benzyl alcohol could be neurotoxic. However, it is not anticipated that high systemic doses of benzyl alcohol will be achieved after clinical use of the lice asphyxiator drug product. No systemic toxicity was noted in 2 week repeat dose dermal toxicology studies conducted with up to 15% lice asphyxiator drug product in rats and dogs. Very limited systemic exposure was achieved in either study with only 1 hour plasma samples yielding measurable levels of benzyl alcohol. The 5% lice asphyxiator drug product caused minor dermal irritation in both rats and dogs after 2 weeks of repeat dermal exposure (6 hours/day).

Benzyl alcohol elicited a positive response in some in vitro genetic toxicology assays and a negative response in other in vitro genetic toxicology assays. No evidence of carcinogenic activity was noted for benzyl alcohol in 2 year oral carcinogenicity studies in rats (doses up to 400 mg/kg benzyl alcohol) or mice (doses up to 200 mg/kg benzyl alcohol) conducted by the National Toxicology Program. Benzyl alcohol was not teratogenic at high doses that elicited maternal toxicity in systemic rat and rabbit embyrofetal development studies.

B. Pharmacologic activity – Lice Asphyxiator (Insecticide, Pediculicide)

C. Nonclinical safety issues relevant to clinical use – None at this time

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

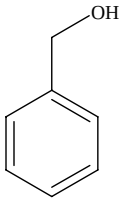
NDA number: 22-129
Review number: 1
Sequence number/date/type of submission: 000 / 6-15-07 / Original NDA submission
Information to sponsor: No
Sponsor and/or agent: Summer Laboratories, Inc.
103 G.P. Clement Dr.
Collegeville, PA 19426

Manufacturer for drug substance: (b) (4)

Reviewer name: Barbara Hill
Division name: Dermatologic and Dental Drug Products
HFD #: HFD-540
Review completion date: 1-10-08

Drug:

Trade name: Not established
Generic name: Lice Asphyxiator (benzyl alcohol), 5%
Code name: N/A
Chemical name: Benzyl alcohol
CAS registry number: 100-51-6
Molecular formula/molecular weight: C_7H_8O (C_6H_5 - CH_2OH) / 108.1
Structure:



Relevant INDs/NDAs/DMFs:

1) IND 50,076 (Lice Asphyxiator; treatment of head lice; DDDP)

Drug class: Preservative, Lice Asphyxiator (Insecticide, Pediculicide)

Intended clinical population: Treatment of *Pediculus humanus capitis* (head lice) of the scalp hair

Clinical formulation:

The quantitative composition of the lice asphyxiator drug product (expressed as %w/w) is provided in the following table.

Ingredient	**5%**	(b) (4)		(b) (4)
Benzyl alcohol, NF	5	(b) (4)		
Mineral oil, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sorbitan monooleate, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Polysorbate 80, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Carbopol 934P, NF*	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Trolamine, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Distilled water	(b) (4)	(b) (4)	(b) (4)	(b) (4)

* - Carbomer 934P was considered an acceptable carbomer for use in this topical drug product during the early phase of development due to the very low levels of benzene (NMT 0.01%). (b) (4)

Concern was raised during the pre-NDA meeting about the possible level of benzene exposure that would occur with use of the lice asphyxiator drug product. (b) (4) In addition, there is a small amount of benzene in carbomer 934P. The sponsor was asked to monitor the amount of benzene in the (b) (4) drug product. (b) (4) .

Based on the information provided in the NDA submission, it appears that the benzene level contributed by (b) (4) carbomer 934P can be up to (b) (4) . Therefore, the drug product does meet the ICH Q3C limit of 2 ppm for benzene in drug products. In addition, subjects will apply this product twice, separated by at least 7 days, for 10 minutes per application. Therefore, very limited exposure to any potential benzene in the drug product would be achieved under conditions of clinical use.

The sponsor has previously stated that (b) (4) benzyl alcohol is the maximum feasible concentration of benzyl alcohol in this formulation.

Route of administration: Topical

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Background:

IND 50,076 was originally submitted to the Division on November 13, 2003. The sponsor is developing the lice asphyxiator drug product for the treatment of head lice. One of the head louse's defenses to prevent asphyxiation from exposure to prolonged rinsing with water is the insect's ability to open and close it's breathing apparatus called spiracles. Lice have a "resurrection response" that enables them to shut these spiracles for a prolonged period of time, even up to 12 hours, and then become active again. Petrolatum has been observed to significantly immobilize and coat the lice long enough for asphyxiation to occur. However, some lice survived after an overnight petrolatum treatment. The sponsor's proposed mechanism of action for their drug product is that the benzyl alcohol functions to keep spiracles (breathing holes) of head lice open so that asphyxiation occurs more rapidly. The sponsor claims that asphyxiation occurs in minutes in the presence of benzyl alcohol. Mineral oil (b) (4) Carbomer 934P is a water soluble polymer (b) (4). This is the first drug product to use benzyl alcohol as an active instead of as a preservative.

An End of Phase 2 meeting was conducted on September 9, 2004. A pre-NDA meeting was conducted on March 12, 2007. The sponsor submitted an electronic CTD NDA submission for the Lice Asphyxiator drug product and has included labeling in the PLR format. This NDA submission is a 505(b)(2) application because the sponsor is relying on literature references to satisfy some aspects of nonclinical toxicology information needed to support the safety of benzyl alcohol (primarily systemic repeat dose toxicology and genetic toxicology). No specific listed drug products are referred to in these literature references.

Studies reviewed within this submission:

All nonclinical toxicology studies conducted to support the lice asphyxiator drug product were submitted and reviewed under the IND. A summary of the information from these studies is provided in this NDA review. The reader is referred to the reviews entered under IND 50,076 in DARRTS if additional detail is necessary. A list of the nonclinical studies conducted with the lice asphyxiator product is provided below for reference purposes.

Submitted in original IND submission

1) A 14-day dermal toxicity study in rats (Study# 3651.1)
2) A 14-day dermal toxicity study in dogs (Study# 0437DS70.001)

The sponsor summarized acute toxicity, repeat dose toxicity, genetic toxicity, carcinogenicity and reproductive toxicity data available for benzyl alcohol based on a comprehensive review of the benzyl alcohol literature that was contained in a Cosmetic Ingredient Review report written by Bindu Nair. The reference for this review article is provided below.

Nair, B. Final report on the safety assessment of Benzyl alcohol, Benzoic acid, and Sodium benzoate. Int. J. Toxicol. 1002; 20 Suppl 3: 23 – 50.

Information from this literature review article is summarized in the appropriate sections of this document. It was determined after review of the original IND submission that the reproductive and developmental toxicology studies conducted with benzyl alcohol that are reported in the literature were not adequate to determine the teratogenic potential of benzyl alcohol. It was recommended that embryofetal developmental studies be conducted in both a rodent and nonrodent species to provide adequate data to address the teratogenic potential of benzyl alcohol. The final study reports for the rat and rabbit embryofetal development studies conducted with benzyl alcohol were submitted in Serial #019 on December 14, 2005.

Submitted in Serial #019 (Date: 12-14-05)

1) A study for effects of benzyl alcohol on embryofetal development in rats (Study# 1129-004)
2) A study for effects of benzyl alcohol on embryofetal development in rabbits (Study# 1129-005)

Studies not reviewed within this submission: N/A

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Two in vitro pharmacology studies were conducted with the lice asphyxiator drug product. In the first in vitro pharmacology study, the pediculocide activity of the lice asphyxiator drug product containing (b) (4) benzyl alcohol (b) (4) was compared to the activity of formulations containing 5% benzyl alcohol or 5% mineral oil. The lice asphyxiator drug product demonstrated virtually complete lice killing activity up to 5 hours post dose. (b) (4)

In the second in vitro pharmacology study, scanning electron microscopy revealed that when lice were exposed to the lice asphyxiator drug product their breathing spiracles remain open allowing the material to occlude the breathing apparatus resulting in death. When lice were exposed to test articles that did not contain benzyl alcohol, the spiracles closed down which allowed the lice to survive.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Lice asphyxiation

Drug activity related to proposed indication: Lice asphyxiation

2.6.2.3 Secondary pharmacodynamics – N/A

2.6.2.4 Safety pharmacology

No nonclinical safety pharmacology studies were conducted with benzyl alcohol. Based on the toxicity profile established for benzyl alcohol in the literature and the results of the 2 week dermal toxicology studies conducted in rats and dogs with the lice asphyxiator drug product, the need for safety pharmacology studies was waived for the lice asphyxiator drug product. No treatment related effects were noted on the electrocardiographic parameters evaluated in the 2 week dermal dog toxicology study.

2.6.2.5 Pharmacodynamic drug interactions – N/A

2.6.3 PHARMACOLOGY TABULATED SUMMARY – N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Toxicokinetic analysis for benzyl alcohol was incorporated into the 2 week dermal toxicology studies conducted in rats and dogs with the lice asphyxiator drug product. This toxicokinetic information is summarized with the results of each study under section 2.6.6.1 "Overall toxicology summary/ general toxicology". The following information was obtained concerning the pharmacokinetics of benzyl alcohol from the following literature source.

Clayton, G.D., F.E. Clayton (eds.) Patty's Industrial Hygiene and Toxicology. Volumes 2A, 2B, 2C, 2D, 2E, 2F: Toxicology. 4th ed. New York, NY: John Wiley & Sons Inc., 1993-1994. 2704

2.6.4.2 Methods of Analysis – N/A

2.6.4.3 Absorption

The dermal flux for benzyl alcohol across human skin in vitro was reported at 0.073 mg/sq cm/hr, indicating a low rate of dermal uptake. The percentage of the applied dose that penetrated through human skin in vitro in 6 hr was 1.42 percent for adult skin and 0.73 percent for full term infant skin.

2.6.4.4 Distribution – N/A

2.6.4.5 Metabolism

Benzyl alcohol is readily absorbed from the gastrointestinal tract and rapidly oxidized (by liver alcohol dehydrogenase) to benzoic acid, which is conjugated with glycine and excreted as hippuric acid in the urine.

2.6.4.6 Excretion

Human subjects eliminated 75 to 85 percent of the dose in the urine as hippuric acid within 6 hr after taking 1.5 g of benzyl alcohol orally.

2.6.4.7 Pharmacokinetic drug interactions – N/A

2.6.4.8 Other Pharmacokinetic Studies

The sponsor submitted the final study report for a clinical pharmacokinetic study titled "Evaluation of the bioavailability of lice asphyxiator 5% in subjects with head lice infestation" (Study SU-01-2007; Report number MC07B-0209) to the NDA on December 28, 2007. Forty-five subjects with head lice infestation were enrolled in this study. Three age cohorts were incorporated into this study (6 months to 3 years; 4 to 11 years; 12 years and older). Nine subjects from each of the three age cohorts were assigned to the 10 minute treatment group and six subjects from each of the three age cohorts were assigned to the 30 minute treatment group. The 5% lice asphyxiator drug product was applied topically in sufficient quantity to fully saturate the hair and scalp for a single 10 minute or 30 minute application. Blood samples for determination of plasma benzyl alcohol concentrations were drawn at the following time points (copied from the study report).

6 months to 3 years (Cohort 1)	1 ml at pre-dose, and 0.5, 1, 3, and 6 hours after completion of application of 5% L.A.
4 to 11 years (Cohort 2)	2 ml at pre-dose and 0.5, 1, 3, 6, and 12 hours after completion of application of 5% L.A.
12 years and older (Cohort 3)	5 ml at pre-dose and 0.5, 1, 2, 3, 6, 9, 12 and 24 hours after completion of application of 5% L.A.

Benzyl alcohol plasma concentrations were determined using a validated HPLC method (lower limit of quantitation = 1 µg/ml). A total of 300 samples were analyzed in this study. The majority of the subject's samples had plasma concentrations of benzyl alcohol below the lower limit of quantitation. Benzyl alcohol concentrations were sporadically noted at 0.5 to 3 hours post dose for all subjects in this study. The study report indicates that no pharmacokinetic analyses were performed due to the paucity of and low benzyl alcohol concentration levels detected in this study.

The study report did not provide the length of hair that was treated or the total amount of the lice asphyxiator drug product that was administered in this study. Therefore, it becomes difficult to determine if this study was conducted under maximal use conditions. The clinical pharmacology reviewer will determine whether this human bioavailability study is acceptable. However, overall it appears that very low systemic absorption of benzyl alcohol occurred after topical application of the lice asphyxiator drug product to the hair and scalp for up to 30 minutes. The very low level to zero systemic exposure to benzyl alcohol after topical application of the lice asphyxiator drug product under conditions of clinical use is in agreement with the very low level of systemic exposure noted after topical administration of the lice asphyxiator drug product (up to 15%; 6 hours/day) for two weeks in rats and dogs (described later in this document).

2.6.4.9 Discussion and Conclusions

No additional nonclinical pharmacokinetic studies are recommended for the lice asphyxiator drug product at this time.

2.6.4.10 Tables and figures to include comparative TK summary – N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY – N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Two week repeat dose dermal toxicology studies were conducted in rats and dogs with the lice asphyxiator drug product. Doses of 0 (untreated control), 0% (vehicle), 5% (100 mg/kg/day), 10% (200 mg/kg/day) and 15% (300 mg/kg/day) lice asphyxiator drug product were used in both studies. Lice asphyxiator drug product was applied for 6 hours/day in both studies. The lice asphyxiator drug product was applied under occlusion in the rat study.

The 5% lice asphyxiator drug product caused minor dermal irritation in both rats and dogs after 2 weeks of repeat dermal exposure (6 hours/day). Both of these studies applied the lice asphyxiator drug product for 6 hours/day for two weeks. In addition, the rat study was conducted under occlusive conditions. Therefore, the conduct of both the rat and dog studies were under exaggerated use conditions compared to the proposed clinical use. The clinical use of the lice asphyxiator drug product will be to apply two ten minute applications of drug product separated by at least one week. The duration and extent of dermal exposure to the lice asphyxiator drug product under conditions of clinical use is much less than was used in the two week dermal toxicology studies conducted in rats and dogs.

Negligible plasma concentrations of benzyl alcohol were detected in the low, mid and high dose groups in the 2 week dermal rat toxicology study. Samples were quantifiable in only the one hour post-dose sample in the mid and high dose groups. The mean one hour plasma concentrations (μg/ml) of benzyl alcohol in rats following daily application of the lice asphyxiator drug product are provided in the following table.

Conc. (% w/w)	Dose (mg/kg/day)	Day 1		Day 14	
		Males	Females	Males	Females
5	100	0.00	0.00	0.00	0.00
10	200	0.44	0.38	1.69	1.08
15	300	1.59	1.42	3.59	2.32

A dose dependent increase in the mean one hour plasma concentrations was noted for the mid and high dose groups. In addition, concentrations increased 1.6 to 3.8 fold after multiple dosing. No apparent gender effect on the mean one hour plasma concentrations was noted in this study. The highest benzyl alcohol exposure was observed in high dose male rats on day 14 with a mean one hour plasma concentration of 3.59 μg/ml.

Negligible plasma concentrations of benzyl alcohol were detected in the low, mid and high dose groups in the 2 week dermal dog toxicology study. Samples were quantifiable in only the one hour post-dose samples. The mean one hour plasma concentrations (µg/ml) of benzyl alcohol in dogs following daily application of the lice asphyxiator drug product are provided in the following table.

Conc. (% w/w)	Dose (mg/kg/day)	Day 1		Day 14	
		Males	Females	Males	Females
5	100	0.00	0.00	2.94	3.24
10	200	0.00	0.60	5.08	6.89
15	300	0.90	0.26	10.2	3.26

A dose dependent increase in the mean one hour plasma concentrations was noted for male animals, but not female animals, on day 14. The mean one hour benzyl alcohol plasma concentrations increased between 3 – 12 fold following 14 days of dosing. No apparent gender effect on the mean one hour plasma concentrations was noted in the low and mid dose groups. An apparent gender effect on the mean one hour plasma concentrations was noted in the high dose group. This may be more of a factor related to an unusually low value in high dose females on days 1 and 14. The highest benzyl alcohol exposure was observed in high dose male dogs on day 14 with a mean one hour plasma concentration of 10.2 µg/ml.

The National Toxicology Program conducted two 13 week oral toxicology studies in rats and mice with benzyl alcohol. These studies were conducted in 1990 and are described below.

Fischer 344 rats (10/sex/dose) were given oral (gavage) doses of 50, 100, 200, 400, and 800 mg/kg technical grade benzyl alcohol (99% pure) (in corn oil) for 13 weeks. The high dose produced clinical signs indicative of neurotoxicity including staggering, respiratory difficulty, and lethargy. Reduction in weight gain was noted in males at 800 mg/kg and females at equal to or greater than 200 mg/kg. The high dose animals also showed hemorrhages around the mouth and nose, and histological lesions in the brain, thymus, skeletal muscle, and kidney.

B6C3F1 mice (10/sex/dose) were given oral (gavage) doses of 50, 100, 200, 400, and 800 mg/kg technical grade benzyl alcohol (99% pure) (in corn oil) for 13 weeks. The high dose appeared to produce clinical signs of neurotoxicity. Reduction in weight gain was noted in males at equal to or greater than 400 mg/kg and females at equal to or greater than 200 mg/kg. No treatment related histopathological effects were noted.

The results from these two studies suggest that high doses of benzyl alcohol could be neurotoxic. However, it is not anticipated that high systemic doses of benzyl alcohol will be achieved after clinical use of the lice asphyxiator drug product. No additional general toxicology studies are recommended for the lice asphyxiator drug product at this time.

Genetic toxicology:

Numerous literature in vitro genetic toxicology studies have been conducted with benzyl alcohol. Benzyl alcohol has produced mixed results in genetic testing. Benzyl alcohol was

negative in the Ames test with and without metabolic activation, sex-linked recessive lethal assay (conducted in flies), and the replicative DNA synthesis assay (conducted in male rats). Negative results were obtained in the mouse lymphoma assay (L5178Y/TK) with metabolic activation, but a positive response was noted in the mouse lymphoma assay without metabolic activation at a concentration producing cellular toxicity. Benzyl alcohol was positive in the Chinese hamster ovary chromosomal aberration assay with metabolic activation. Equivocal results were noted in the sister chromatid exchange assay conducted with benzyl alcohol.

Benzyl alcohol elicited a positive response in some genetic toxicology assays and a negative response in other genetic toxicology assays. An in vivo mouse micronucleus assay has not been conducted with benzyl alcohol. However, the need for this assay is waived since oral carcinogenicity studies have been conducted in mice and rats with benzyl alcohol.

Carcinogenicity:

Literature carcinogenicity studies conducted with benzyl alcohol are summarized below.

A skin painting study was performed in mice (60/sex/group) using a hair dye containing 2% benzyl alcohol. Two control groups of animals received the same shaving procedure but were not treated with any test article. The treated group of animals received 50 µl of the test article on a shaved skin treatment site, three times weekly for 20 months. No effects on body weight or survival were noted in this study. No treatment related increase in neoplasms was noted in this study.

The National Toxicology Program conducted oral (gavage) carcinogenicity studies with benzyl alcohol in rats and mice.

Fischer 344 rats (50/sex/dose) were given oral (gavage) doses of 0, 200 and 400 mg/kg technical grade benzyl alcohol (99% pure) (in corn oil), 5 days/week, for 2 years. Decreased survival was noted in the females at both doses, but not in the males. However, many of these deaths were considered to be gavage errors. No adverse effects on body weight gain were noted in this study. No treatment related increase in the incidence of any neoplasms was noted in this study. The National Toxicology Program concluded that there was no evidence of carcinogenic activity of benzyl alcohol in male or female rats.

B6C3F1 mice (50/sex/dose) were given oral (gavage) doses of 0, 100, and 200 mg/kg technical grade benzyl alcohol (99% pure) (in corn oil), 5 days/week, for 2 years. No treatment related effects on survival or body weight were noted in this study. No treatment related increase in the incidence of any neoplasms was noted in this study. The National Toxicology Program concluded that there was no evidence of carcinogenic activity of benzyl alcohol in male or female mice.

In summary, the National Toxicology Program concluded that under the conditions of these 2 yr gavage studies, there was no evidence of carcinogenic activity of benzyl alcohol for male or female F344/N rats dosed with 200 or 400 mg/kg. Survival in both dose groups of female rats was 50% that of vehicle controls, primarily due to an increase number of gavage

related deaths. There was no evidence of carcinogenic activity of benzyl alcohol for male or female B6C3F1 mice dosed with 100 or 200 mg/kg for 2 years. No additional carcinogenicity studies are recommended for benzyl alcohol.

Reproductive toxicology:

Literature reproductive and developmental studies conducted with benzyl alcohol are summarized below.

CD-1 mice (50/sex/group) received oral (gavage) doses of 0 or 750 mg/kg/day benzyl alcohol (in distilled water) on gestation days 7 – 14. Earlier toxicity studies had determined that the maximum tolerated dose in CD-1 mice was between 645 and 1300 mg/kg/day benzyl alcohol. Therefore, the 750 mg/kg/day dose was selected for this study based on that information. The animals were allowed to deliver their litters and were sacrificed on lactation day 3. Treatment related maternal deaths (18/50) were noted in the benzyl alcohol treated group in this study. Clinical signs in benzyl alcohol treated animals included tremors, hunching, subdued behavior, prostration, ataxia, swelling and/or cyanosis of the abdomen, and piloerection. Maternal body weight was significantly lower in benzyl alcohol treated animals compared to control animals. No treatment related effects on reproductive parameters or gestation indices were noted in this study. Pup weights in the benzyl alcohol treated group were decreased compared to control pups on Lactation day 1. Mean litter weight gain in the benzyl alcohol treated group was decreased compared to the control group on lactation days 1 – 3. The investigators for this study considered benzyl alcohol a suspect reproductive hazard and recommended further investigation.

In a second study, CD-1 mice (50/sex/group) received oral (gavage) doses of 0 or 750 mg/kg/day benzyl alcohol on gestation days 6 – 13. The animals were allowed to deliver their litters and were sacrificed on lactation Day 3. Litter size, birth weight and neonatal growth and survival to postnatal day 3 were measured in this study. Nineteen (38%) of the dams of the benzyl alcohol group died prior to necropsy. No maternal deaths were noted in the control group. Maternal weight was significantly decreased (↓21.5%) in benzyl alcohol treated animals compared to control animals. In addition, fetal birth weigh and three day weight gain were significantly decreased in the benzyl alcohol treated group compared to the control group.

In a third study, pregnant female CD-1 mice (50/group) received oral (gavage) doses of 0 or 500 mg/kg/day benzyl alcohol (in corn oil) on gestation days 6 – 15. No treatment related effects on survival, bodyweight gain, gestation index, reproductive index, postnatal survival, average litter weight or average pup weight were noted in this study.

A literature reference included in the original IND submission provided a description of a study which determined the teratogenic activity of ethinyl-estradiol sulfonate in Wistar rats. Apparently, a vehicle control group was incorporated into this study that was treated with benzyl alcohol dissolved in peanut oil. Intraperitoneal injections of benzyl alcohol (dose not specified in literature article) were administered to rats (number of rats not specified in literature article) on gestational days 10, 13, 6 – 10 or 10 – 14. Fetuses were removed on gestation day 21 and examined for teratogenic effects. No teratogenic effects were noted in this study.

The three literature reproductive and developmental studies conducted in CD-1 mice did not evaluate the teratogenic potential of benzyl alcohol. The literature teratogenicity study conducted in Wistar rats that included a benzyl alcohol control group is not adequate. The actual benzyl alcohol dose used in this study was not provided and the dosing duration did not incorporate the appropriate timeframe (i.e., gestational days 6 – 15). Therefore, the teratogenic potential of benzyl alcohol has not been evaluated adequately based on the literature studies conducted to date.

The following information was obtained from the REPROTOX database concerning Benzyl alcohol.

Benzyl alcohol has been used as a preservative in bacteriostatic medical solutions. Its use in neonates (particularly premature babies) has been associated with neurologic abnormalities and death. It is no longer used under such circumstances.

Since benzyl alcohol shows signs of being a neurotoxicant in repeat dose animal toxicology studies and in human neonates, it was determined that embyrofetal developmental toxicology studies should be conducted in a rodent and non-rodent species to better define the dose range where this may present a potential hazard and determine the teratogenic potential associated with benzyl alcohol. Therefore, it was recommended that embryofetal developmental toxicology studies be conducted in a rodent and non-rodent species to determine the teratogenic potential associated with benzyl alcohol prior to conduct of Phase 3 clinical studies.

The sponsor submitted the final study reports for subcutaneous rat and rabbit embryofetal development studies (with corresponding dose range findings studies) conducted with benzyl alcohol in Serial #019 (date: 12-14-05) of the IND. The reader is referred to the review of this submission in DARRTS if additional detail is needed. Toxicokinetic analysis was performed in subcutaneous dose range finding studies conducted in pregnant Sprague-Dawley and pregnant White New Zealand rabbit. A summary of the results from these studies is provided below.

Subcutaneous doses of 0 (vehicle: corn oil), 100, 250, 500 and 1000 mg/kg/day benzyl alcohol (dose volume: 2 ml/kg) were administered to pregnant female Sprague-Dawley rats (main study: 5 females/dose; TK: 9 females/group) from gestation days 6 – 17 in the rat dose range finding study. Significant maternal mortality was noted at the 1000 mg/kg/day dose. Therefore, the high dose was selected as 500 mg/kg/day in the definitive rat embryofetal development study. Plasma samples for toxicokinetic analysis were collected on gestation days 6 and 17. A summary of the mean toxicokinetic parameters obtained from this study is provided in the following table.

Dose (mg/kg/day)	C_{max} (µg/ml)	T_{max} (hr)	$AUC_{0\text{-}24\ hr}$ (µg·hr/ml)
Gestation day 6			
100	12.0	0.5	10.3
250	18.3	0.5	22.7
500	35.9	0.5	57.3
1000	45.9	0.5	155.1
Gestation day 17			
100	7.1	0.5	6.8
250	15.9	0.5	21.1
500	28.0	0.5	33.6
1000	ND	ND	ND

ND – not determined (high dose group terminated early due to high mortality)

An approximate dose dependent increase in systemic exposure was noted with increased dose. No apparent dose accumulation was noted over the treatment period.

Subcutaneous doses of 0 (vehicle: corn oil), 100, 250 and 500 mg/kg/day benzyl alcohol (dose volume: 2 ml/kg) were administered to pregnant female Sprague-Dawley rats (25 females/group) from gestation days 6 – 17 in the definitive rat embryofetal development study. The dose range used in this study appeared to be adequate. Maternal toxicity was noted in high dose animals (decreased body weight {↓8.4%} and body weight gain {↓16.9%} over gestation days 6 – 20 compared to control animals). In addition, fetal body weight for both sexes was decreased in the high dose group (↓17%) compared to the control group. This may have been due to the maternal toxicity (decreased body weight in high dose does). The NOEL for maternal and fetal toxicity was 250 mg/kg/day benzyl alcohol ($AUC_{0\text{-}24\ hr}$ = 21.1 µg·hr/ml on gestation day 17) after subcutaneous administration during gestation days 6 – 17 in rats. No other treatment related effects on fetal parameters or on soft tissue or skeletal abnormalities (malformations or variations) were noted in this study. The NOEL for teratogenicity was 500 mg/kg/day benzyl alcohol ($AUC_{0\text{-}24\ hr}$ = 33.6 µg·hr/ml on gestation day 17) after subcutaneous administration during gestation days 6 – 17 in rats.

Subcutaneous doses of 0 (vehicle: corn oil), 100, 250, 500 and 1000 mg/kg/day benzyl alcohol (dose volume: 2 ml/kg) were administered to pregnant female White New Zealand rabbits (main study: 5 females/dose; TK: 3 females/group) from gestation days 6 – 18 in the rabbit dose range finding study. Significant maternal mortality was noted in the high dose group. The high dose was decreased from 1000 mg/kg/day to 750 mg/kg/day to 650 mg/kg/day during the first few days of dosing and significantly mortality was still noted in the high dose group. Therefore, the high dose was selected as 400 mg/kg/day in the definitive rabbit embryofetal development study. Plasma samples for toxicokinetic analysis were collected on gestation days 6 and 18. A summary of the mean toxicokinetic parameters obtained from this study is provided in the following table.

Dose (mg/kg/day)	C_{max} (µg/ml)	T_{max} (hr)	$AUC_{0\text{-}24\ hr}$ (µg·hr/ml)
Gestation day 6			
100	28.0	0.5	26.0
250	48.9	0.5	75.4
500	76.6	1.0	182.6
1000	129.3	0.8	395.3
Gestation day 18			
100	18.1	0.5	18.2
250	33.5	0.8	58.5
500	37.1	0.8	141.0
1000	ND	ND	ND

ND – not determined (high dose group terminated early due to high mortality)

A slightly greater than dose dependent increase in systemic exposure was noted with increased dose. No apparent dose accumulation was noted over the treatment period.

Subcutaneous doses of 0 (vehicle: corn oil), 100, 250 and 400 mg/kg/day benzyl alcohol (dose volume: 2 ml/kg) were administered to pregnant female New Zealand White rabbits (23 females/group) from gestation days 6 – 18 in the definitive rabbit embryofetal development study. The dose range used in this study appeared to be adequate. Maternal toxicity was noted in high dose animals (mortality {7/23}, decreased body weight {↓7.0%}, decreased body weight gain {↓30.9%} and increased incidence of clinical signs {decreased activity, breathing difficulties, feces few/absent and thin appearance}) and mid dose animals (mortality {2/23} and decreased body weight gain {↓20.0%}). The NOEL for maternal toxicity was 100 mg/kg/day benzyl alcohol ($AUC_{0\text{-}24\ hr}$ = 18.2 µg·hr/ml on gestation day 18) after subcutaneous administration during gestation days 6 – 18 in rabbits.

Decreased fetal body weight (↓9% for both sexes combined) was noted in the high dose group. This may have been due to the maternal toxicity. The NOEL for fetal toxicity was 250 mg/kg/day benzyl alcohol after subcutaneous administration during gestation days 6 – 18 in rabbits ($AUC_{0\text{-}24\ hr}$ = 58.5 µg·hr/ml on gestation day 18). No teratogenicity was noted in this study. The NOEL for teratogenicity is 400 mg/kg/day benzyl alcohol ($AUC_{0\text{-}24\ hr}$ = 141.0 µg·hr/ml on gestation day 18 for the 500 mg/kg/day benzyl alcohol dose in the dose range finding study) after subcutaneous administration during gestation days 6 – 18 in rabbits.

The dose range tested in both studies appeared to be adequate due to the maternal toxicity noted in the high dose groups for both studies. It was determined that the results of the submitted systemic rat and rabbit embyrofetal development studies indicated that benzyl alcohol was not teratogenic at high doses that elicited maternal toxicity in both species. The clinical reviewer was informed that it would be acceptable to enroll women of childbearing potential in Phase 3 clinical studies for the lice asphyxiator drug product from a pharmacological/toxicological perspective. Due to the very low systemic exposure noted in repeat dose dermal toxicology

studies, it was determined that fertility and peri- and post-natal development studies are waived for the lice asphyxiator drug product.

Special toxicology:

Undiluted benzyl alcohol was moderately irritating when applied to the depilated skin of guinea pigs for 24 hr. It was moderately irritating when applied to rabbit skin. Benzyl alcohol was severely irritating to the eyes of rabbits. There have been a few literature reports of hypersensitivity reactions to benzyl alcohol when used as a preservative.

The sponsor provided final study reports for 2 week repeat dose dermal toxicology studies in rats and dogs conducted with the lice asphyxiator drug product in the original IND submission. The sponsor also provided a summary of the acute toxicity, repeat dose toxicity, genetic toxicity, carcinogenicity and reproductive toxicity data available for benzyl alcohol from the literature in the original IND submission. Based on the evaluation of all of the toxicology data provided in the original IND submission, the need for a nonclinical toxicology study in juvenile rodents, covering the period of maturation, prior to allowing treatment of pediatric patients with the lice asphyxiator drug product was waived. In addition, since dermal irritation was evaluated in the 2 week dermal rat and dog toxicology studies conducted with the lice asphyxiator drug product, the need for nonclinical dermal and ocular irritation studies were waived for the lice asphyxiator drug product. Since the lice asphyxiator drug product is a wash off product that will be left on the scalp for only two 10 minute applications separated by at least one week, the need for a nonclinical photoirritation study was waived for the lice asphyxiator drug product.

2.6.6.2 Single-dose toxicity – N/A

2.6.6.3 Repeat-dose toxicity – N/A

2.6.6.4 Genetic toxicology – N/A

2.6.6.5 Carcinogenicity – N/A

2.6.6.6 Reproductive and developmental toxicology – N/A

2.6.6.7 Local tolerance – N/A

2.6.6.8 Special toxicology studies – N/A

2.6.6.9 Discussion and Conclusions

The lice asphyxiator NDA is a 505(b)(2) submission since the sponsor relied on literature data for the repeat dose systemic toxicity and genotoxicity associated with benzyl alcohol.

The National Toxicology Program conducted two 13 week oral (gavage) toxicology studies with benzyl alcohol in rats and mice. The results from these 13 week repeat dose oral

toxicology studies suggest that high doses of benzyl alcohol could be neurotoxic. However, it is not anticipated that high systemic doses of benzyl alcohol will be achieved after clinical use of the lice asphyxiator drug product.

The sponsor conducted 2 week repeat dose dermal toxicology studies with up to 15% lice asphyxiator drug product in rats and dogs. No systemic toxicity was noted in either study. Very limited systemic exposure was achieved in either study with only 1 hour plasma samples yielding measurable levels of benzyl alcohol. The 5% lice asphyxiator drug product caused minor dermal irritation in both rats and dogs after 2 weeks of repeat dermal exposure (6 hours/day). The 5% lice asphyxiator drug product was identified as the dermal NOAEL in both rats and dogs. Both of these studies applied the lice asphyxiator drug product for 6 hours/day for two weeks. In addition, the rat study was conducted under occlusive conditions. Therefore, the conduct of both the rat and dog studies were under exaggerated use conditions compared to the proposed clinical use. The clinical use of the lice asphyxiator drug product will be to apply two ten minute applications of drug product separated by at least one week. The duration and extent of dermal exposure to the lice asphyxiator product under conditions of clinical use will be much less than was used in the two week dermal toxicology studies conducted in rats and dogs.

The systemic NOAEL in both the rat and dog studies was identified as 15% lice asphyxiator drug product (300 mg/kg/day; 1800 mg/m^2/day in rats; 6000 mg/m^2/day in dogs), the maximum dose possible based on maximum feasible concentration. The clinical reviewer, Dr. Gordona Diglisic, informed me that the maximum amount of lice asphyxiator drug product that will be applied is 6 – 8 oz bottles (total 48 oz) to hair that is >22 inches. The 48 oz application is equivalent to a 1440 ml application of the 5% lice asphyxiator drug product. This would equal a dose of 1200 mg/kg/day (44400 mg/m^2/day) benzyl alcohol for a 60 kg individual (adult) and a dose of 7200 mg/kg/day (144000 mg/m^2/day) benzyl alcohol for a 10 kg individual (child). The multiple of human exposure based on the systemic NOAEL noted in rats and dogs would range from 0.04 – 0.14X in adults and 0.01 – 0.04X in children. These multiples of human exposure do not accurately represent the safety based on systemic exposure to benzyl alcohol since systemic exposure to benzyl alcohol was minimal after 2 weeks of dermal administration of the lice asphyxiator drug product in rats and dogs. Plasma concentrations of benzyl alcohol were quantifiable in only the one hour post-dose samples (highest plasma concentration in rats after 14 days = 3.59 μg/ml; highest plasma concentration in dogs after 14 days =10.2 μg/ml). Human use would be a maximum of two 10 minute applications separated by at least 7 days. Therefore, it is anticipated that the multiples of human exposure would be much greater based on actual systemic exposure to benzyl alcohol under conditions of clinical use.

The sponsor submitted a final study report for a clinical pharmacokinetic study to the NDA on December 28, 2007. The results from this study were previously summarized under Section 2.4.6.8 “Other Pharmacokinetic Studies”. Even though it may be difficult to determine if this clinical pharmacokinetic study was conducted under maximal use conditions because the study report did not provide the length of hair that was treated or the total amount of the lice asphyxiator drug product that was administered in this study, overall it appears that very low systemic absorption of benzyl alcohol occurred after topical application of the lice asphyxiator drug product to the hair and scalp for up to 30 minutes.

No AUC values could be calculated for benzyl alcohol in either the 2 week dermal rat and dog toxicology studies or the clinical pharmacokinetic study conducted with the lice asphyxiator drug product due to low systemic plasma levels of benzyl alcohol that were noted only at 1 hr post dose in the animal studies and sporadically in the clinical pharmacokinetic study. Therefore, it is not possible to calculate the multiples of human exposure based on AUC comparison for the 2 week dermal rat and dog toxicology studies or for the rat and rabbit embryofetal development studies (summarized below). Calculation of the multiple of human exposure based on the total amount of drug applied and expressed as mg/m^2 (i.e., body surface area) provides a very low multiple of human exposure ratio which is not an accurate reflection of systemic exposure due to the low systemic absorption of benzyl alcohol after topical administration in humans. Inclusion of these exaggerated multiples of human exposure values in the label for the lice asphyxiator drug product would not provide useful information to evaluate the safety of the lice asphyxiator drug product.

Numerous literature in vitro genetic toxicology studies have been conducted with benzyl alcohol. Benzyl alcohol has produced mixed results in genetic testing. Benzyl alcohol was negative in the Ames test with and without metabolic activation, sex-linked recessive lethal assay (conducted in flies), and the replicative DNA synthesis assay (conducted in male rats). Negative results were obtained in the mouse lymphoma assay (L5178Y/TK) with metabolic activation, but a positive response was noted in the mouse lymphoma assay without metabolic activation at a concentration producing cellular toxicity. Benzyl alcohol was positive in the Chinese hamster ovary chromosomal aberration assay with metabolic activation. Equivocal results were noted in the sister chromatid exchange assay conducted with benzyl alcohol.

Benzyl alcohol elicited a positive response in some in vitro genetic toxicology assays and a negative response in other in vitro genetic toxicology assays. An in vivo mouse micronucleus assay has not been conducted with benzyl alcohol. However, the need for this assay is waived since oral carcinogenicity studies have been conducted in mice and rats with benzyl alcohol.

The National Toxicology Program conducted two oral (gavage) carcinogenicity studies with benzyl alcohol in rats and mice. The National Toxicology Program concluded that under the conditions of these 2 yr gavage studies, there was no evidence of carcinogenic activity of benzyl alcohol for male or female F344/N rats dosed with 200 or 400 mg/kg. Survival in both dose groups of female rats was 50% that of vehicle controls, primarily due to an increase number of gavage related deaths. There was no evidence of carcinogenic activity of benzyl alcohol for male or female B6C3F1 mice dosed with 100 or 200 mg/kg for 2 years.

It was determined that adequate data was not available in the literature to adequately address the teratogenic potential of benzyl alcohol. The sponsor conducted subcutaneous rat and rabbit embryofetal developments studies with benzyl alcohol. The dose range tested in both studies appeared to be adequate due to the maternal toxicity noted in the high dose groups for both studies (i.e., 500 mg/kg/day in rats and 400 mg/kg/day in rabbits). It was determined that the results of the submitted systemic rat and rabbit embyrofetal development studies indicated that benzyl alcohol was not teratogenic at high doses that elicited maternal toxicity in both species. Due to the very low systemic exposure noted in repeat dose dermal toxicology studies,

it was determined that fertility and peri- and post-natal development studies are waived for the lice asphyxiator drug product.

No additional nonclinical toxicology studies are recommended for the lice asphyxiator drug product.

2.6.6.10 Tables and Figures – N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY – N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Based on the nonclinical data available for benzyl alcohol, NDA 22-129 for the lice asphyxiator drug product is approvable from a pharmacology/toxicology perspective provided that the recommended changes in the label discussed below are incorporated into the lice asphyxiator drug product label.

Unresolved toxicology issues (if any):

There are no unresolved toxicology issues for NDA 22-129, at this time.

Recommendations:

It is recommended that the suggested labeling changes provided in the next section be incorporated into the lice asphyxiator drug product label.

Suggested labeling:

For reference purposes, the dose ratio values (multiples of human exposure) based on body surface area comparisons (assuming 100% systemic absorption) between various species and man following exposure to the lice asphyxiator drug product are provided in the following table. It was presumed that the maximum daily dose of the lice asphyxiator drug product is 1440 ml/day (i.e., 6 – 8 oz bottles equals 48 oz of lice asphyxiator drug product) for these calculations.

Species/Sex	Route	Dose (mg/kg/day)	Km factor	Dose (mg/m^2)	Dose ratio
Embryofetal development studies					
Rat	sc	100	6	600	0.014
		250	6	1500	0.034
		500	6	3000	0.068
Rabbit	sc	100	12	1200	0.027
		250	12	3000	0.068
		400	12	4800	0.108
Carcinogenicity studies					
Rat	oral	200	6	1200	0.027
		400	6	2400	0.054
Mouse	oral	100	3	300	0.007
		200	3	600	0.014
Human	Topical	1200[a]	37	44400	--

a – assuming a 60 kg individual with a maximum daily dose of 1440 ml/day of the lice asphyxiator drug product and assuming 100% systemic absorption (1440 ml lice asphyxiator drug product/day x 50 mg benzyl alcohol/ml lice asphyxiator drug product ÷ 60 kg = 1200 mg/kg/day benzyl alcohol for an adult subject).

In summary, the multiples of human exposure for all of the reproductive toxicology studies and carcinogenicity studies conducted with benzyl alcohol range from 0.007 – 0.108. These values are all well below 1 since they are based on a comparison of the total applied dose. In addition, these values are based on assuming daily administration of the lice asphyxiator drug product, which is a condition that greatly exaggerates the clinical conditions of use (i.e., apply two 10 minute wash off administrations separated by at least one week). Therefore, basing the multiples of human exposure on body surface area comparisons yields values that are not representative of the true clinical use of the lice asphyxiator drug product. Also, it is not possible to calculate multiples of human exposure based on AUC comparisons due to low systemic plasma levels of benzyl alcohol that were noted sporadically in the clinical pharmacokinetic study conducted with the lice asphyxiator drug product. Therefore, it is difficult to make traditional multiple of human exposure calculations for this drug product due to the limited exposure under conditions of clinical use. It may be most appropriate and least confusing to put actual doses used in each nonclinical study in the label with no multiple of human exposure values for this drug product. A comment about the low systemic exposure noted in the clinical pharmacokinetic study which did not allow for calculation of AUC values should be included in the label to provide a rationale for the absence of multiple of human exposure values.

The sponsor calculated multiples of human exposure based on mg/kg in the label for the teratogenicity studies. It is not clear how the sponsor performed these calculations. The multiples of human exposure calculated by the sponsor should be removed from the label.

The sponsor included a label for the lice asphyxiator drug product in the PLR format in the NDA submission. The nonclinical portions of the lice asphyxiator drug product label are provided below. It is recommended that the highlighted wording be inserted into and the ~~strikeout~~ wording be deleted from the "Pregnancy" and "Carcinogenicity, Mutagenesis, Impairment of Fertility" sections of the lice asphyxiator drug product label.

8. USE IN SPECIFIC POPULATIONS

Note: No comparisons of animal exposure with human exposure are provided in this product information due to the low systemic exposure noted in the clinical pharmacokinetic study [*See Clinical Pharmacology (12.3)]* which did not allow for determination of human AUC values that could be used for this calculation.

8.1. Pregnancy

Pregnancy Category B. (b) (4)

~~P~~Pregnant rats were dosed with ~~B~~benzyl ~~A~~alcohol via subcutaneous injection at 100, 250, and 500 mg/kg/day. No teratogenic effects were noted at any dose. Maternal toxicity occurred at 500 mg/kg/day. (b) (4)

Pregnant rabbits received subcutaneous injections of (b) benzyl (b) (4) alcohol at 100, 250, and 400 mg/kg/day. No teratogenic effects were noted at any dose. (b) (4)

There are no adequate or well controlled studies with benzyl alcohol in pregnant women. (b) (4)

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, mutagenesis, impairment of fertility

Long term studies in animals to evaluate carcinogenic potential of (b) (4) TRADENAME have not been conducted. No evidence of carcinogenic activity was noted for benzyl alcohol in 2 year oral carcinogenicity studies in rats (doses up to 400 mg/kg benzyl alcohol) or mice (doses up to 200 mg/kg benzyl alcohol) conducted by the National Toxicology Program. (b) (4)

—

(b) (4)

Benzyl alcohol has produced mixed results in genetic testing. Benzyl alcohol was negative in the Ames test with and without metabolic activation, sex-linked recessive lethal assay, and the replicative DNA synthesis assay (conducted in male rats). Negative results were obtained in the mouse lymphoma assay with metabolic activation, but a positive response was noted in the mouse lymphoma assay without metabolic activation at a concentration producing cellular toxicity. Benzyl alcohol was positive in the Chinese hamster ovary chromosomal aberration assay with metabolic activation. (b) (4)

No fertility studies have been conducted with benzyl alcohol.

(b) (4)

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

cc:
DDDP/DIV DIR/WALKER
DDDP/PHARM SUP/BROWN
DDDP/PHARM/HILL
DDDP/MO/DIGLISIC
DDDP/PM/BAUERLIEN

APPENDIX/ATTACHMENTS

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

/s/

Barbara Hill
2/19/2008 07:16:26 AM
PHARMACOLOGIST

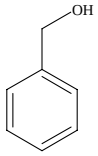
Paul Brown
2/19/2008 12:56:34 PM
PHARMACOLOGIST

Pharmacology/Toxicology Memorandum

To: NDA 22-129
From: Barbara Hill, Ph.D., Pharmacology/Toxicology Supervisor

Re:

Submission date: 10-17-08
Serial No.: N 000 AZ
Submission type: Complete Response to Approvable Letter
Drug: [Tradename] (benzyl alcohol) lotion, 5%; Lice asphyxiator
Molecular formula: C_7H_8O (C_6H_5 - CH_2OH)
Molecular weight: 108.1
Structure:



Drug class: Preservative, Lice asphyxiator (Insecticide, Pediculicide)
Indication: Treatment of *Pediculus humanus capitis* (head lice) of the scalp hair
Route: Topical
Sponsor: Summer Laboratories, Inc., Collegeville, PA

Review date: January 30, 2009

Clinical formulation:

The quantitative composition of the lice asphyxiator drug product (expressed as %w/w) is provided in the following table.

Ingredient	**5%**	(b) (1)	(b) (1)	**Function**
Benzyl alcohol, NF	5	(b) (1)	(b) (1)	Active
Mineral oil, NF	(	(	(	(b) (4)
Sorbitan monooleate, NF	(b)	(b)	(b)	(b) (4)
Polysorbate 80, NF	(b)	(b)	(b)	(b) (4)
Carbopol 934P, NF*	(b)	(b)	(b)	(b) (4)
Trolamine, NF	(b)	(b)	(b)	(b) (4)
Distilled water	(b) (4)	(b) (4)	(b) (4)	(b) (4)

* - Carbomer 934P was considered an acceptable carbomer for use in this topical drug product during the early phase of development due to the very low levels of benzene (NMT 0.01%). (b) (4)

Concern was raised during the pre-NDA meeting about the possible level of benzene exposure that would occur with use of the lice asphyxiator drug product. (b) (4)

In addition, there is a small amount of benzene in carbomer 934P. The sponsor was asked to monitor the amount of benzene in the (b) (4) drug product. (b) (4)

Based on the information provided in the NDA submission, it appears that the benzene level contributed by (b) (4) carbomer 934P can be up to (b) (4) Therefore, the drug product does meet the ICH Q3C limit of 2 ppm for benzene in drug products. In addition, subjects will apply this product twice, separated by at least 7 days, for 10 minutes per application. Therefore, very limited exposure to any potential benzene in the drug product would be achieved under conditions of clinical use.

The sponsor has previously stated that (b) (4) benzyl alcohol is the maximum feasible concentration of benzyl alcohol in this formulation.

Introduction:

NDA 22-129 was originally submitted under section 505(b)(2) of the FD&C Act with a letter date of June 15, 2007. This NDA submission is a 505(b)(2) application because the sponsor is relying on literature references to satisfy some aspects of nonclinical toxicology information needed to support the safety of benzyl alcohol (primarily systemic repeat dose toxicology and genetic toxicology). No specific listed drug products are referred to in these literature references. In addition, the sponsor conducted 14-day dermal toxicity studies with the lice asphyxiator drug product in rats and dogs and oral embryofetal development studies with benzyl alcohol in rats and rabbits. Based on the nonclinical data submitted to NDA 22-129 for benzyl alcohol and the lice asphyxiator drug product, Pharmacology/Toxicology recommended approval of NDA 22-129 provided that the recommended changes in the label described in the review were incorporated into the drug product label. The reader is referred to the Pharmacology/Toxicology review of the original NDA entered into DFS on February 19, 2008 for additional details, if needed.

The NDA was found to be Approvable and an Approvable Letter (that contained issues that needed to be addressed for approval and FDA draft recommended wording) was sent to the sponsor on July 14, 2008. There were no pharmacology/toxicology issues in the Approvable Letter. A Complete Response to the Approvable Letter was submitted to NDA 22-129 on October 17, 2008. No new nonclinical data was submitted in this resubmission.

A summary of the issues identified in the approvable letter and the sponsor's corresponding responses are provided below.

1) Provide a reason for the sporadic elevated plasma concentrations of benzyl alcohol (> 3 mcg/ml) noted in the maximal use clinical pharmacokinetic study.

The sponsor indicated in the submission that the reason for the sporadic elevated plasma concentrations of benzyl alcohol were due to an intermittent use of a bacteriostatic saline (NaCl plus 0.9% benzyl alcohol) catheter flush. Therefore, the sponsor believes that the sporadic elevated plasma concentrations of benzyl alcohol were not true, representative plasma concentrations. The sponsor notes that unfortunately, the phlebotomists involved with the study did not adequately document the use of the benzyl alcohol containing flush. Therefore, the sponsor conducted a second clinical bioavailability study in which any catheter flush used was free of benzyl alcohol. The study report for this study was included in the submission. The sponsor states that the results from the second bioavailability study demonstrated very limited absorption of benzyl alcohol and no elevated benzyl alcohol plasma concentrations approximating the sporadic results seen in the first bioavailability study. The clinical pharmacology and clinical reviewers will determine the adequacy of the submitted data to address this issue.

2) Discuss the relationship between the plasma levels of benzyl alcohol and infant gasping syndrome.

The sponsor included an expert opinion from Dr. Neil Buist in the submission. Apparently Dr. Neil Buist is the lead investigator that identified the occurrence and cause of "gasping syndrome" which is a condition confined to pre-mature babies exposed to multiple iv flushes containing benzyl alcohol over the course of several days. The sponsor indicates that Dr. Buist states that the plasma benzyl alcohol levels in the clinical pharmacokinetic studies conducted with the 5% benzyl alcohol lice asphyxiator drug product are orders of magnitude removed from that which caused gasping syndrome. In addition, Dr. Buist's opinion is that the lice asphyxiator product is perfectly immune from producing the gasping syndrome in the indicated population.

The sponsor also submitted a review authored by the (b) (4) of publicly available benzyl alcohol safety data. Apparently, this evaluation includes a discussion of gasping syndrome in infants and the use of benzyl alcohol in numerous topical cosmetic and drug products. The sponsor believes that this review provides additional support for the safety of their 5% benzyl alcohol lotion product used for the treatment of lice infestations in pediatric patients. The clinical reviewer will determine the adequacy of the submitted information to address this issue.

3) Submit draft labeling that incorporates the wording contained in the Approvable letter.

The sponsor included revised draft labeling in this submission. The sponsor states that the Division's comments have been incorporated into the present versions of the package insert, carton label, immediate container label and patient direction leaflet. The sponsor also indicates that labeling has been updated to reflect the data for the second clinical bioavailability study. The adequacy of the nonclinical portions of the submitted draft label is addressed in the next section of this document.

4) Your container/closure proposal, consisting of an orifice reducing plug (b) (4) and current cap, should be implemented.

The sponsor states that the orifice reducing plug and cap will be implemented per the specifications provided in Sequence 0013. The chemistry and clinical reviewers will determine the adequacy of the sponsor's response to address this issue.

5) If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

The sponsor states that no additional information relating to safety or effectiveness has become available and that the label has been updated to reflect the data collected in the second clinical bioavailability study. The clinical reviewer will determine the adequacy of the sponsor's response to address this issue.

6) During a recent inspection of the manufacturing facility for this application, our field investigator conveyed deficiencies to the facilities representative. Satisfactory resolution to these deficiencies is required before this application may be approved.

The sponsor states that a final response to the PAI inspection deficiencies was forwarded to the (b) (4) by the API manufacturer on August 26, 2008. The sponsor states that they have been informed by the (b) (4) that the response is under review. The sponsor states that the (b) (4) manufacturing facility has indicated it is ready for re-inspection. The chemistry reviewer will determine the adequacy of the sponsor's response to address this issue.

7) A safety update should be included in the complete response to Approvable Letter submission.

The sponsor states that their is no new safety information to report. The clinical reviewer will determine the adequacy of the sponsor's response to address this issue.

8) Provide English translations of current approved foreign labeling not previously submitted.

The sponsor states that there is no foreign labeling to submit. The clinical reviewer will determine the adequacy of the sponsor's response to address this issue.

9) Submit promotional materials for review.

The sponsor states that they intend to request advisory comments on the proposed introductory advertising and promotional material. The clinical reviewer will determine the adequacy of the submitted promotional material provided to address this issue.

Labeling recommendations:

The nonclinical portions of the labeling for the 5% benzyl alcohol lotion product included in this submission are provided below. The sponsor has incorporated the recommended nonclinical wording contained in the original Pharmacology/Toxicology review (entered into

DFS on February 19, 2008; Primary reviewer: Dr. Barbara Hill), the Maternal Health Team review (entered into DFS on January 27, 2009; Reviewer: Dr. Leyla Sahin; Note: A draft of this review was sent to the Division on June 25, 2008. The draft was not different than the final review entered into DFS.) and the tertiary Pharmacology/Toxicology review (entered into DFS on July 11, 2008; Reviewer: Dr. Abby Jacobs, Pharmacology/Toxicology Associate Director). No additional content changes are recommended for the nonclinical portions of the label for the 5% benzyl alcohol lotion product included in this submission. However, I do have one recommended format change for the submitted labeling which is to break the information contained in section 13.1 into three paragraphs (as provided below) instead of two paragraphs (as contained in the submitted labeling) for easier reading of the label.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies with topical benzyl alcohol in pregnant women. Reproduction studies conducted in rats and rabbits were negative. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

No comparisons of animal exposure with human exposure are provided in this labeling due to the low systemic exposure noted in the clinical pharmacokinetic study [see *Clinical Pharmacology* (12.3)] which did not allow for the determination of human AUC values that could be used for this calculation.

Pregnant rats were dosed with benzyl alcohol via subcutaneous injection at 100, 250, and 500 mg/kg/day. No teratogenic effects were noted at any dose. Maternal toxicity and decreased fetal weight occurred at 500 mg/kg/day. When pregnant rabbits received subcutaneous injections of benzyl alcohol at 100, 250, and 400 mg/kg/day, there were no teratogenic effects in offspring at any dose. In rabbits, maternal toxicity occurred at the two higher doses and was associated with decreased fetal weight at the highest dose.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals to evaluate carcinogenic potential of TRADENAME Lotion have not been conducted. No evidence of carcinogenic activity was noted for benzyl alcohol in 2 year oral carcinogenicity studies in rats (doses up to 400 mg/kg benzyl alcohol) or mice (doses up to 200 mg/kg benzyl alcohol) conducted by the National Toxicology Program.

Benzyl alcohol has produced mixed results in genetic testing. Benzyl alcohol was negative in the Ames test with and without metabolic activation, sex-linked recessive lethal assay, and a replicative DNA synthesis assay (conducted in male rats). Negative results were obtained in the mouse lymphoma assay with metabolic activation, but a positive response was noted in the mouse lymphoma assay without metabolic activation at a concentration producing a high level of cellular toxicity. Benzyl alcohol was positive in the Chinese hamster ovary chromosomal aberration assay with metabolic activation.

No fertility studies have been conducted with benzyl alcohol.

Conclusions:

This NDA can be approved from a Pharmacology/Toxicology perspective.

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/s/

Barbara Hill
1/30/2009 04:45:17 PM
PHARMACOLOGIST

Comments on N22-129 Lice asphyxiator, benzyl alcohol lotion

From Abby Jacobs, Pharm/Tox AD
July 11, 2008

I concur that there are no nonclinical approval issues for this product.
I concur that the appropriate pregnancy category is B.

I have a couple of small labeling recommendations.

The statement on the equivocal sister chromatid exchange finding—(b) (4) should be removed, since the genetic significance of SCE results is not understood and thus we don't mention such findings in labeling. We also don't mention equivocal findings in labeling. See below for suggestions.

Benzyl alcohol has produced mixed results in genetic toxicity testing. Benzyl alcohol was negative in the Ames test with and without metabolic activation, sex-linked recessive lethal assay, and a replicative DNA synthesis assay (conducted in male rats). Negative results were obtained in the mouse lymphoma assay with metabolic activation, but a positive response was noted in the mouse lymphoma assay without metabolic activation at a concentration producing a high degree of cellular toxicity. Benzyl alcohol was positive in the Chinese hamster ovary chromosomal aberration assay with metabolic activation.

There is an extra "the" in the last line of 8.1. In rabbits, maternal toxicity occurred at the two higher doses and was associated with decreased fetal weight at the highest dose.

(b) (4)

I have discussed these comments with the acting team leader and he concurs.

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/s/

Abby Jacobs
7/11/2008 01:52:14 PM
PHARMACOLOGIST