CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-129

OFFICE DIRECTOR MEMO

MEMORANDUM

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

DATE: April 9, 2009

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 22-129 TRADENAME (benzyl alcohol) Lotion, 5%
Sciele Pharma, Inc.

Summary

TRADENAME (benzyl alcohol) Lotion, 5% is a topical pediculoside. Benzyl alcohol acts by stunning the respiratory spiracles of human head lice open, allowing the vehicle to obstruct the spiracles and causing the lice to asphyxiate. This memo documents my concurrence with the Division of Dermatology and Dental Product's (DDDP's) recommendation for the approval of the NDA for TRADENAME (benzyl alcohol) Lotion, 5%, for the topical treatment of head lice infestation in patients 6 months of age and older.

Description and Dosing

TRADENAME (benzyl alcohol) Lotion, 5%, is a white topical lotion containing benzyl alcohol, 5%, as the active ingredient. The inactive ingredients in this formulation are water, mineral oil, sorbitan monooleate, polysorbate 80, carbomer 934P, and trolamine. The lotion is applied to dry hair, using enough to completely saturate all hair and scalp. It is left on for 10 minutes, and then thoroughly rinsed off with water. Treatment is repeated after 7 days. Eye exposure should be avoided. TRADENAME (benzyl alcohol) Lotion, 5%, should only be used on pediatric patients under the direct supervision of an adult.

Regulatory History[1]

NDA 22-129 was originally submitted on June 15, 2007 as a 505(b)(2) application. Benzyl alcohol is an active ingredient for over-the-counter use as an anorectal analgesic, and is an excipient in approved drug products, including solutions for intravenous administration. TRADENAME (benzyl alcohol) Lotion, 5%, however, is the first drug product to contain benzyl alcohol as an active ingredient and is considered a new molecular entity. FDA took an approvable action on July 14, 2008 citing the following deficiencies that would need to be addressed prior to approval: 1) clarification regarding the significance of high, albeit sporadic, plasma concentrations of benzyl alcohol in a maximal use systemic exposure study (SU-01-2007), 2) implementation of the proposed container/closure system (orifice reducing plug and cap) to avoid accidental ingestion, and 3) satisfactory resolution of deficiencies noted on inspection of the drug substance manufacturing facility. The applicant submitted a complete response to the approvable letter on October 17, 2008. The NDA was not presented to the Dermatology and Ophthalmology Drugs Advisory Committee because the systemic exposure to benzyl alcohol following topical treatment with TRADENAME (benzyl alcohol) Lotion, 5%, was low and no concerning safety signals were documented.

Efficacy

The efficacy of TRADENAME (benzyl alcohol) Lotion, 5%, was evaluated in two vehicle-controlled randomized trials in 628 patients, aged 6 months and older, with active head lice infestation. Treatment was applied two times separated by one week. Efficacy was assessed as the proportion of patients who

[1] Additional information regarding the regulatory history of NDA 22-129 may be found in the review of Daniel Shames dated July 14, 2008.

were free of live lice 14 days after the final treatment. The majority of patients (76.2 and 75.0%, respectively, in the two trials) receiving benzyl alcohol treatment were free of live lice 14 days after treatment. In contrast, only 4.8% and 26.2%, respectively, of patients receiving vehicle control in these trials were lice-free.

Safety

A total of 478 benzyl alcohol-treated patients and 336 vehicle-treated patients were evaluable for safety. The occurrence of new onset skin, scalp and ocular toxicity was monitored in clinical trials. Among patients who developed toxicity on treatment, the event rates in benzyl alcohol-treated as compared to vehicle-treated patients were: pruritus, 12% vs. 4%; erythema, 10% vs. 9%; pyoderma, 7% vs. 4%; and ocular irritation, 6% vs. 1%. Application site reactions were uncommon.

Although not indicated for neonatal use, the product labeling for TRADENAME (benzyl alcohol) Lotion, 5%, will carry a warning regarding the risk of neonatal gasping syndrome that has been associated with intravenous administration of products containing benzyl alcohol. This syndrome consists of severe metabolic acidosis, gasping respirations, and central nervous system depression. Seizures, intracranial hemorrhage, hypotension, hepatic and renal failure, and death may occur in preterm, low birth weight infants. Although expected systemic exposure of benzyl alcohol from proper use of TRADENAME (benzyl alcohol) Lotion, 5%, is substantially lower than that reported in association with the gasping syndrome, the minimum amount of benzyl alcohol at which toxicity may occur is not known. Thus, neonates (i.e., infants less than 1 month of age or preterm infants with a corrected age of less than 44 weeks) could be at risk for gasping syndrome if treated with TRADENAME (benzyl alcohol) Lotion, 5%.

Chemistry, Manufacturing, and Controls

Adequate information has been provided regarding raw materials controls, manufacturing process and process controls, specifications for assuring consistent product quality, and the container/closure system. Upon re-inspection, the drug substance manufacturing facility satisfactorily met cGMP requirements.

Clinical Pharmacology Issues

The applicant determined that saline preserved with benzyl alcohol was used as a flush for the intravenous catheters placed in patients for pharmacokinetic sampling in study SU-01-2007, and that this practice likely resulted in the observed sporadic plasma elevations of benzyl alcohol. The applicant conducted a repeat maximal use systemic exposure study of similar design (Sc-LA-08-01) in 19 patients with head lice infestation. TRADENAME (benzyl alcohol) Lotion, 5%, was applied at three times the normal exposure period. Four patients had quantifiable plasma levels, all of which were below 3 mcg/ml, which is significantly lower than the plasma levels identified in neonates with gasping syndrome.

Tradename Review

The tradename for this product is not resolved at this time. The proposed tradenames (b) (4) and (b) (4) were not deemed acceptable based on promotional concerns. The proposed tradenames (b) (4), (b) (4), (b) (4), and (b) (4) were not deemed acceptable due to potential name confusion with marketed products that could lead to medication errors. Specifically, DDDP concurs with the concerns raised by the Division of Medication Errors and Analysis regarding potential confusion of **(b) (4)**

The applicant has been requested to submit an alternative tradename.

Required Pediatric Assessments

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The applicant has fulfilled the pediatric study requirement for ages 6 months to 18 years for this application. Pediatric studies are waived for neonates (0-1 month) because necessary studies would be impossible or highly impracticable since there are too few neonates with head lice to study. Pediatric studies are also waived for pediatric patients 1-6 months of age since the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. Head lice infestation is not prevalent in children younger than six months of age and the standard treatment for children that age is to shave the head.

Postmarketing Requirements under 505(o)

No postmarketing studies or clinical trials will be required under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007.

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Director,
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/s/

Julie Beitz

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DIRECTOR