CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022259Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	18 September 2015
From	Kendall A. Marcus, M.D.
Subject	Division Director Summary Review
NDA #	22259
Applicant Name	Hill Dermaceuticals, Inc.
Date of Submission	18 December 2014
PDUFA Goal Date	18 September 2015
Proprietary Name / Established (USAN) Name	Tolak Cream, 4% 5-fluorouracil cream, 4%
Dosage Forms / Strength	Cream, 4%
Proposed Indication(s)	Topical treatment of actinic keratosis of face, ears and scalp
Action	18 September 2015

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Amy Woitach, MD
Statistical Review	Kathleen Fritsch, PhD
Pharmacology Toxicology Review	Barbara Hill, PhD
CMC Review	Jane Chang, PhD
CMC Microbiology Review	LCDR Jessica Cole, PhD
Clinical Pharmacology Review	Doanh Tran, PhD
DPV Review	Jessica Weintraub, RPh
OSE/DMEPA Review	Carlos Mena-Grillasca, RPh
OPDP Review	Tara Turner, Pharm.D., MPH
DMPP Review	Sharon Mills, BSN

OND=Office of New Drugs
CMC= Chemistry, Manufacturing and Controls
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs

1. Introduction

In this application, the Sponsor seeks marketing approval for Tolak (5-fluorouracil) Cream, 4%, a new concentration and formulation of 5-fluorouracil (5-FU) for the treatment of actinic keratosis under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act for the treatment of actinic keratosis. Actinic keratosis (AK) lesions are skin-colored to reddish brown or yellowish black ill-defined macules or papules that occur on sun-exposed areas of the skin. They vary in size from pinhead to several centimeters in diameter. AK lesions are the result of cumulative ultraviolet radiation and may be precursors of squamous cell carcinoma of the skin. They generally occur in middle-aged or elderly fair-skinned individuals.

5-FU is a pyrimidine analogue that works against AK lesions by competitively inhibiting the enzyme thymidylate synthase, thereby creating a thymine deficiency and resulting in inhibition of DNA synthesis and cytotoxicity. 5-FU was first observed to have an impact on actinic keratosis during the use of systemic 5-FU for the treatment of cancer. There are several currently marketed 5-FU topical products indicated for the treatment of actinic keratosis, Fluoroplex, Efudex and Carac. The applicant relied on findings of systemic safety for the referenced Efudex Cream 5% in combination with clinical and pharmacokinetic comparability studies to support the safety and effectiveness of Tolak Cream, 4%.

2. Background

NDA 22259 was originally submitted on August 17, 2007. Two Phase 3 trials were conducted and submitted as the basis of efficacy demonstration and were reviewed in the initial cycle. One open-label, long-term follow-up study was also conducted. All review teams with the exception of CMC recommended that this application be approved. In June 2009, the applicant was issued a Complete Response letter citing deficiencies in the application related to product quality and facility inspections. The Complete Response letter did not list any issues regarding the clinical trials.

The CMC review completed during the first review cycle was amended in a review addendum dated June 18, 2008, by Dr. Shulin Ding. The recommendation for approval was changed based on the lack of cGMP compliance in the manufacture of the proposed product; without acceptable cGMP compliance, the identity, strength, purity, and quality of the product could not be assured.

As outlined in a second CMC review entered into DFS in May 2009, the September 2008 establishment inspection revealed major deficiencies in cGMP compliance as well as deficiencies in the drug product stability data. Out of specification (OOS) results were reported for two recently produced lots of bulk drug and one lot of the packaged product. These OOS results suggested that the manufacturing process was not well controlled.

The Complete Response submitted on December 18, 2014, included information needed to address the product quality and facility inspection deficiencies listed in the Complete Response letter. The applicant also updated their proposed labeling to include results from a 12-month follow-up study.

3. CMC

Please refer to the product quality review by Jane Chang, Ph.D for full details of the review. This NDA is now recommended for approval from a CMC perspective. An overall recommendation of "Approve" was made by the Facility reviewer, Donald Lech, on September 17, 2015.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review for this resubmission was conducted by Barbara Hill, PhD; please see her review for full details. No nonclinical toxicology studies were conducted to support the original NDA submission or the NDA resubmission. The sponsor included literature references in the original NDA submission that address the toxicology of 5-FU. Because the sponsor was able to generate a clinical bridge to Efudex cream, this NDA is submitted as a 505(b)(2) submission.

The nonclinical toxicology of systemically or topically administered 5-FU has been established previously in the literature. The main adverse effects noted with parenterally or orally administered 5-FU are on the rapidly proliferating cells of the bone marrow and the gastrointestinal tract and include leukopenia, stomatitis, gastrointestinal ulceration and bleeding, and severe diarrhea. Central neurotoxicity, myocardial effects, liver effects and effects on the skin, have also occurred after parenteral administration in animals and humans. Following topical application, effects observed at the dermal administration site have included local inflammatory reactions, photosensitivity and hyperpigmentation.

Numerous articles exist in the literature describing the mutagenicity of 5-FU. Many of these articles indicate that fluorouracil has genotoxic effects in both mammalian and non-mammalian systems. Compounds such as fluorouracil that have an effect on DNA, RNA and protein synthesis are expected to have positive effects on mutagenicity and chromosomal damage. Most of the studies conducted to address the carcinogenic potential of 5-FU that are reported in the literature are inadequate. However, based on the strong genotoxicity signal noted in the literature, it is anticipated that fluorouracil would prove to be a carcinogenic agent in appropriately designed and conducted nonclinical carcinogenicity studies. The Division determined that the treatment of actinic keratosis with topical fluorouracil is not a chronic indication due to the extensive irritation at the treatment site. Therefore, carcinogenicity studies are not needed for Tolak cream.

Systemic fluorouracil treatment elicited teratogenic effects in mice, rats and hamsters and embryolethality in hamsters and monkeys. Systemic fluorouracil treatment induced chromosomal aberrations and changes in chromosome organization of spermatogonia in rats which resulted in transient infertility in male rats. Systemic fluorouracil treatment elicited negative effects on female fertility in rats (significantly reduced the incidence of fertile matings, delayed the development of preimplantation and postimplantation embryos, increased the incidence of preimplantation lethality and induced chromosomal anomalies in these embryos). Teratogenic effects have been noted in humans after topical application of Efudex cream and systemic administration of fluorouracil. Tolak cream should be labeled as a Pregnancy Category X drug as is the label for Efudex cream. It has been determined that the Tolak cream label will not be revised to conform with the Pregnancy Labeling and Lactation Rule (PLLR) at this time.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was conducted by Dr. Tapash Ghosh during the first review cycle and completed on April 18, 2008, with an approval recommendation. Please see his review for complete details. A study was conducted by the applicant to compare the steady state plasma concentration of 5-FU after application of Tolak Cream, 4% versus Efudex in subjects with actinic keratoses. Overall systemic absorption was low and appeared similar in subjects treated with Tolak Cream, 4% as compared to Efudex. This study, in combination with the literature support provided for the non-clinical requirements, established an acceptable bridge for Tolak Cream, 4% to Efudex for a 505(b)2 application.

Dr. Doanh Tran recommended minor labeling changes during his review of this resubmission.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The original application contained two Phase 3 trials, Study 48 and Study 49, designed to assess the efficacy and safety of Tolak Cream, 4% for the treatment of AK. The two studies combined enrolled 403 subjects on the Tolak arm. Statistical and clinical reviews conducted during the first review cycle concluded that the efficacy of Tolak cream 4% had been demonstrated as compared to vehicle control. The conclusions of the original statistical and clinical reviews are unchanged following review of the resubmission. The primary efficacy endpoint results (100% clearance of lesions 4 weeks post-treatment for Tolak Cream 4% versus vehicle) for Studies 48 and 49 are presented in Table 1, reprinted from the statistical review of Kathleen Fritsch, PhD. Please see her review for full details.

Table 1 – 100% Clearance Rates (Studies 48 and 49)

	Tolak 4%	Vehicle	p-value
Study 048	N=353	N=70	
100% Clearance	192 (54%)	3 (4%)	<0.001
Study 049	N=50	N=50	
100% Clearance	12 (24%)	2 (4%)	0.004

The treatment effect for the clearance rate was much higher in Study 048 than 049. The reason for this is unclear.

The applicant also updated their proposed labeling to include results (b) (4) The results from this study

were not submitted in time during the first review cycle to permit substantive review of the data.

The applicant used complex definitions of recurrence and non-recurrence to analyze the data from this study, which made interpretation of study results difficult. Kathleen Fritsch, PhD, the statistical reviewer for this application, concluded that subjects should be classified as to whether they remained clear, had a recurrence or received alternate treatments, or were lost to follow-up at 12 months. Table 3 summarizes outcomes from Study 50 as conducted by Dr. Fritsch.

Table 3 - Recurrence Assessment in Study 50 (Labeling Recommendation)

	N=204
Remained clear 12 months later	56 (27%)
Recurrence within 12 months or had other treatments applied	110 (54%)
No follow-up	38 (19%)

8. Safety

The safety review was completed by David Kettl, M.D. during the first review cycle with an approval recommendation. Please see his review for complete details.

As a drug product, 5-FU is a well-established molecular entity with an adverse event profile that is well described through decades of clinical use. Common side effects are predictable and related to topical application of the product; erythema, scaling/dryness, crusting, pruritis, stinging/burning, edema and erosions. Adverse reactions observed in Study 50, the long-term study, were similar to those observed in the two Phase 3 studies. Most of the skin neoplasms observed in Study 50 occurred in non-treated areas and were considered unrelated to the application of 5-FU.

One 77 year old male who completed 28 applications of study medications was noted the next week to have basal cell carcinoma at four different sites (left hand, left ear, right chest and right forehead). The lesions on his left ear and right chest were already adequately treated with the study medication; 5-FU is an approved treatment for basal cell carcinoma. The lesions on his left hand and right forehead were treated with curettage and electrodessication five months later.

9. Advisory Committee Meeting

Not applicable; this application was not presented to the Advisory Committee as the application did not raise novel or controversial issues that would merit outside discussion.

10. Pediatrics

Pediatric studies are waived for this product because the conduct of such studies would be highly impractical. Actinic keratoses occur almost exclusively in the adult population and are uncommon before middle age.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Proposed labeling was reviewed during the first review cycle. Additional revisions were made during the resubmission based on analysis of the 12-month follow-up study. The proposed container labels, carton labeling and Full Prescribing Information were evaluated by Carlos Mena-Grillasca of DMEPA; labeling revisions were made based on his recommendations. Patient labeling was reviewed by Sharon Mills of DMPP.

13. Decision/Action/Risk Benefit Assessment

Regulatory action: Approval

I concur with the recommendations of the multi-disciplinary review team regarding approval of NDA 22259 Tolak Cream, 4% for the treatment of the actinic keratosis.

Risk-benefit assessment: The applicant established the efficacy and safety of Tolak Cream, 4% in the treatment of actinic keratosis in two adequate and well-controlled trials, and provided sufficient information in their application to support product labeling. The efficacy of the product justifies the modest risks, which appear to be primarily the risk for local skin reactions.

Postmarketing Risk Evaluation and Management Strategies: Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not required.

Postmarketing requirements (PMR) and commitments (PMC): none

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/s/

KENDALL A MARCUS
09/18/2015