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RESEARCH**

APPLICATION NUMBER:

022259Orig1s000

OTHER REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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Division of Pediatric and Maternal Health Review

Date: September 3, 2015 **Consult Received:** April 24, 2015

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Office of Drug Evaluation IV (ODE IV)

Through: Tamara Johnson, MD, MS, Acting Team Leader
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Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health, ODE IV

To: Division of Dermatology and Dental Products

Drug: Tolak (5-fluorouracil) Cream, 4%, NDA 22-259

Proposed Indication: Tolak Cream is a nucleoside metabolic inhibitor indicated for the topical treatment of actinic keratosis lesions of the face, ears, and scalp.

Subject: Labeling Review

Sponsor: Hill Dermaceuticals, Inc.

Consult Request: “DDDP would like to seek your input on PLLR language added to the draft label in an amendment dated 2-19-15.”

INTRODUCTION

On December 17, 2014, Hill Dermaceuticals, Inc. submitted this NDA for Tolak Cream (5-fluorouracil), 4% Topical (NDA 22-259) as a 505(b)(2) application referencing the innovator product Efudex Cream (5% 5-fluorouracil), NDA 16-831 approved in June, 1970. The Division of Dermatology and Dental Products (DDDP) consulted the Division of Pediatric and Maternal Health Staff - Maternal Health Team (DPMH) to review and provide labeling recommendations for the Pregnancy and Lactation Labeling Rule (PLLR) format for Tolak Cream.

BACKGROUND

Regulatory History

This application has a long history beginning in 2007 and is notable for submission of fraudulent manufacturing assay data. A Consent Decree was issued in 2011 against Hill Dermaceuticals, but was revoked at the end of 2014 for one of the applicant's NDAs, Tolak Cream. Specific dates and FDA actions for this application are listed in the table below.

August 20, 2007	Original NDA submission
June 10, 2008	Site Inspection Report notes significant deviations from cGMP found. Withhold approval recommended.
April 27, 2009	Warning Letter issued
June 22, 2009	Complete Response issued
November 30, 2011	Consent Decree issued against Hill Dermaceuticals
Nov 12, 2014	Consent Decree revoked for Tolak Cream NDA
December 18, 2014	NDA Resubmission Complete Class 2
March 24, 2015	Major Amendment received March 24, 3 month extension to Sept 18, 2015

Actinic Keratosis

Actinic keratosis is a precancerous skin lesion which is most common in sun exposed areas of the body.¹ Actinic keratoses are prevalent, occurring in 10 to 25% of Americans. There are multiple treatment modalities for actinic keratoses including topical application of cytotoxic drugs, cryosurgery, electrosurgery, dermabrasion and excision. Seven topically applied fluorouracil drug products are currently available (see Appendix). There is also a combination of both pharmaceutical and non-pharmaceutical treatment which uses a porphyrin-based topical solution of aminolevulinic acid, which induces cell lysis when illuminated with a particular wavelength, and energy of light emitted by the Blue Light Photodynamic Therapy Illuminator (NDA 20-965).

Clinical Pharmacology of Fluorouracil

Fluorouracil is an antimetabolite pyrimidine analog which causes cytotoxicity.^{2,3} The floxuridine triphosphate (FUdR) metabolite is incorporated into RNA, blocking processing

¹ Kaur R, Alikhan A, Maibach H. Comparison of topical 5-fluorouracil formulations in actinic keratosis Treatment. J Dermat Treatmt 2010;21:267-271. DOI: 10.3109/09546630903341937

² Drug Monograph Access Medicine: <http://accessmedicine.mhmedical.com/drugs.aspx?globalId=6215> Accessed March 27, 2014

and mRNA translation.⁴ Fluorouracil is a prodrug that requires a complex series of biotransformations to produce its active deoxyribosyl and ribosyl nucleotide metabolites.⁵ The fluorodeoxyuridine monophosphate (F-dUMP) metabolite inhibits thymidylate synthase and depletes stores of thymidine triphosphate essential for DNA synthesis.^{6,7} These disruptions to DNA and RNA mediated events are cytotoxic and are the basis of fluorouracil's effectiveness against rapidly proliferating malignant cells.⁸ Based on its mechanism of action, fluorouracil is a teratogenic drug when administered parenterally.

Systemic Exposure from Topically Applied Fluorouracil

To evaluate the teratogenic risk of a topical drug product, data is needed on the quantity of drug that reaches the systemic circulation. The applicant provided data which is briefly described in the Tolak Cream Clinical Pharmacology (12.3) subsection of the labeling.⁹ Twenty-one patients with at least three actinic keratosis lesions on their head or neck were treated with Tolak Cream. The drug product was applied once daily to the lesion and surrounding skin. For example, if the patient had a lesion near their nose on the left cheek, Tolak Cream was applied to the patient's entire cheek. The patients' lesions were treated for a four week period and plasma fluorouracil concentrations were determined at 9 time points within 24 hours after the last dose. Eight of the 21 patients had undetectable levels of plasma fluorouracil (lower limit of quantification 1.00 ng/mL). The 15 patients for whom plasma fluorouracil could be quantified had a peak drug concentration "generally observed at one hour" after the final dose. The mean peak concentration was 3.66 (\pm 1.58 ng/mL) with a range of 1.11 to 7.34 ng/mL. An estimate of the quantity of Tolak Cream applied to the study patients was not provided nor was the proportion of drug quantity applied topically compared to drug quantity measured in the systemic circulation.

Labeling for the reference product Efudex Cream¹⁰ reports that one gram of ¹⁴C-labeled Efudex cream (5% formulation) was applied to the patients' faces in their systemic absorption study. The labeling notes that "approximately 5.98% of the topical dose was absorbed systemically" and, if applied twice daily, systemic absorption of topical 5% fluorouracil would be "in the range of 5 to 6 mg per daily dose of 100 mg." The Efudex labeling also states that negligible amounts of labeled drug were found in urine and expired CO₂ after three days of treatment with labeled Efudex Cream.

³ Chabner BA, Bertino J, Cleary J, Ortiz T, Lane A, Supko JG, Ryan D. Chapter 61. Cytotoxic Agents. In: Brunton LL, Chabner BA, Knollmann BC. eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e*. New York, NY: McGraw-Hill; 2011.

⁴ See Drug Monograph Access Medicine.

⁵ See Chabner, *et al.*

⁶ See Drug Monograph Access Medicine.

⁷ See Chabner, *et al.*

⁸ See Chabner, *et al.*

⁹ Draft labeling for Tolak Cream.

¹⁰ Efudex Cream (NDA 16831) labeling revised May, 2014, per DailyMed, U.S. Library of Medicine

Exposure Relationship of Intravenous vs. Topical Fluorouracil Administration

To interpret the human and non-clinical data from intravenously administered fluorouracil, DPMH queried the DDDP Clinical Pharmacology team for an estimate of the ratio of the C_{max} from the maximum recommended dose (MRD) of fluorouracil administered intravenously relative to the C_{max} for Tolak Cream applied topically. The DDDP Clinical Pharmacology team estimated the C_{max} for intravenous fluorouracil may be 160,000 ng/mL following a 12 mg/kg dose to a maximum of 800 mg/ day. This estimate was derived from data in three Abbreviated New Drug Applications.¹¹ The intravenous fluorouracil exposure from the MRD (160,000 ng/mL) may be as much as 40,000 times greater than that from once daily topically applied Tolak Cream with a maximum concentration of 3.66 ng/mL.

Topical Fluorouracil Application to Intravaginal or Perineal Regions

For more than three decades topical formulations of fluorouracil have been applied intravaginally to the vaginal mucous membrane or to the perineum to treat condylomata acuminata.¹² The quantity of fluorouracil absorbed from the vaginal mucosa is likely higher than that absorbed from the same topical formulation applied to the face due to the increased moisture which increases drug permeability.^{13,14} These factors must be considered when case reports of adverse pregnancy outcomes, such as those below, are reported following intravaginal administration of topical fluorouracil products.

REVIEW OF AVAILABLE DATA

Animal Data

There are no animal reproduction studies for Tolak Cream or Efudex Cream. Animal data for Efudex Cream were based on the parenteral formulation of fluorouracil which reported embryofetal toxicity at doses of fluorouracil lower than the human therapeutic dose. In mice and rats embryoletality was observed as well as malformations including cleft palate, skeletal defects and deformed appendages. In monkeys, maternal doses of fluorouracil higher than an approximate human dose of 12 mg/kg on a mg/M² basis resulted in abortions. Fertility was also affected in both female and male animals noted as a decrease in the number of fertile matings in female mice and abnormal spermatogenesis (i.e. chromosomal aberrations and changes in chromosomal organization of spermatogonia in rats) with decreased sperm count in male mice. The decreased sperm count in male mice was described as transient but no evaluation of whether fertility recovered in female mice is reported.

¹¹ Data from ANDAs 40278, 40333, and 40334

¹² Hull M, Bowen-Simpkins P, Paintin D. Topical treatment of vaginal intraepithelial neoplasia. *Obstet and Gynecol* 1977;??:382

¹³ Burkhart C, Morrell D, Goldsmith L. Burkhart C, Morrell D, Goldsmith L Burkhart, Craig, et al. Chapter 65. Dermatological Pharmacology. In: Brunton LL, Chabner BA, Knollmann BC. Brunton L.L., Chabner B.A., Knollmann B.C. Eds. Laurence L. Brunton, et al.eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e. New York, NY: McGraw-Hill; 2011. Accessed June 20, 2015.

<http://accesspharmacy.mhmedical.com/content.aspx?bookid=374&Sectionid=41266278>

¹⁴ Clinical Pharmacology online. Accessed July2, 2015

<http://www.clinicalpharmacology-ip.com/Forms/Common/print.aspx?cpnum=258&sec=mo...>

Reviewer's comment: The animal data for this section of the Tolak Cream labeling are derived from studies completed in the 1960s. These studies were not designed to conform to current regulatory requirements.

Human Data References

There are no adequate epidemiological or case-control studies evaluating the teratogenicity of fluorouracil in pregnant women, whether the drug is administered topically or intravenously. There are a limited number of case reports following prenatal exposure to topical fluorouracil exposure. All of these reports were from off-label intravaginal or perineal application of a topical fluorouracil formulation and are summarized below.

Van Le L, Pizzuti D, et al. Accidental use of low-dose 5-fluorouracil in pregnancy. J Reprod Medicine 1991;36:872-874.

- Five women were treated with topical fluorouracil in the lower genital tract, four intravaginally, one externally on the labia minora. Doses ranged from 1 to 2.5 grams per application.
- Timing of exposures
 - three of the pregnancies were between the third and seventh weeks gestation (during organogenesis)
 - one pregnancy between 12 and 16 weeks gestation (after organogenesis completed)
 - one pregnancy 5FU applied externally weekly for the first 16 weeks of gestation (during organogenesis)
- Outcomes
 - one infant exposed during organogenesis had a 47, XXX karyotype obtained via amniocentesis
 - four infants had prenatal ultrasounds with no malformations reported
 - all women delivered healthy appearing infants

Odom L, Plouffe L, Butler W. 5-Fluorouracil exposure during the period of conception: Report on two cases. Am J Obstet Gynecol 1990;163:76-7.

- 26 year old woman treated with 65 mg of 5% fluorouracil cream daily for three days at days 15, 16, 17 post conception with vaginal and cervical application.
 - Embryo exposed between days 15 and 21 post-conception (estimated)
 - 21 week ultrasound fetal anatomic survey – normal
 - Outcome: 3.7 kg at term, last report at six months infant was developing normally.
- 21 year old woman with Systemic Lupus Erythematosus on Plaquenil and prednisone, treated with 65 mg 5% fluorouracil cream intravaginal application daily for four days
 - Fluorouracil exposure occurred at the ‘time of conception’
 - 18.5 weeks normal anatomic survey by ultrasound
 - Amniocentesis showed normal 46, XY karyotype
 - Outcome: Infant had normal developmental milestones at 21 months

Pride G. Treatment of Large Lower Genital Tract Condylomata Acuminata with Topical 5-Fluorouracil. J Repro Medicine 1990;35: 384-387.

- four patients were pregnant at the time of proposed topical fluorouracil treatment, one elected termination
- Remaining three pregnancies were in the third trimester at the time of fluorouracil treatment.
- Outcomes
 - Normal infants were delivered – no adverse events for the neonates were reported.

Hull M, Bowen-Simpkins P, Paintin D. Topical treatment of vaginal intraepithelial neoplasia. Obstet and Gynecol 1977;49:382.

- Pregnant patient treated with topical fluorouracil prior to conception
- Patient was immunosuppressed for renal allograft, concomitant meds reported: prednisone, azathioprine.
- Outcome
 - Normal infant delivered at 37 weeks without abnormality

One report of a women treated with intravenous fluorouracil during pregnancy is also of interest.

Stephens J, Golbus M, *et al.*, Multiple congenital anomalies in a fetus exposed to 5-fluorouracil during the first trimester. Am J Obstet Gynecol.1980;137:747-749.

- 41 year old woman diagnosed with metastatic colon cancer.
- Intravenous fluorouracil treatment started after organogenesis
 - treatment started at 11 – 12 fetal weeks
 - treated with 600 mg daily for five days per week, treated for one month until pregnancy diagnosed (suprapubic mass was observed)
- Concomitant procedures or meds included:
 - bowel x-ray films, chest films, cholangiogram at the second fetal week
 - Estimated less than five rad exposure to fetus – unlikely to ‘cause significant harm’
 - at 8 fetal weeks mother underwent exploratory laparotomy with large bowel resection, tumor extending into mesentery and at least one lymph node
 - Mother treated with tetracycline for a urinary tract infection late in the first trimester
- Elective abortion at 16 fetal weeks: fetus with multiple congenital anomalies:
 - radial aplasia bilaterally, absent thumbs, some absent digits, atresia of esophagus, portions of duodenum, biliary atresia, imperforate anus, common bladder and rectum, renal dysplasia, etc.
 - No karyotype - unable to obtain cells, reduced amniotic fluid
- Outcome/Conclusion:
 - Fetus with multiple congenital malformations. Aneuploidy suspected due to advanced maternal age and 5FU administered after organogenesis. While drug did not cause malformations, 5FU may have affected growing fetal structures already malformed from genetic/genomic defect.

Review of Teratology and Lactation Databases

There are few human data on which to base an assessment of teratogenic risk from topical application of fluorouracil in pregnant women. The TERIS¹⁵ review of fluorouracil states that the risk of teratogenesis is undetermined due to the paucity of data; however, the risk may be substantial based on fluorouracil's inhibition of DNA synthesis. The review also notes that there is variable absorption of topical formulations of fluorouracil.

Sources reviewed to provide background for the Lactation subsection (8.2) include Hale's Medications and Mother's Milk¹⁶ which lists fluorouracil's (route of administration not specified) lactation risk as "Possibly Hazardous." Hale's notes that there are no data available on the transfer of this drug to human milk. LactMed®¹⁷ comments on the intravenous use of fluorouracil stating that most sources consider nursing to be contraindicated during maternal antineoplastic drug therapy. However, topical fluorouracil was reported as posing negligible risk for the breastfed infant when care is taken that the infant's skin or mouth does not come into direct contact with the topically treated areas.

DISCUSSION

Pregnancy Labeling

This 505(b)(2) application relies upon the data, both human and animal, of the Efudex Cream innovator product approved in 1970. Like Efudex Cream, the proposed Tolak Cream labeling includes reports of infants born with birth defects following prenatal exposure to intravenous fluorouracil. An excerpt from the Efudex Cream labeling is included below for reference.

One birth defect (cleft lip and palate) has been reported in the newborn of a patient using Efudex as recommended. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when Efudex was applied to mucous membrane areas. Multiple birth defects have been reported in a fetus of a patient treated with intravenous fluorouracil.¹⁸

This reviewer was unable to find the report of the infant born with a cleft lip and palate following maternal application of Efudex Cream as cited in the current labeling. A search of the original Efudex Cream application for this case report was also unsuccessful. Whether the information for this case originated from published literature or an adverse event reported to the FDA or sponsor is unknown. Therefore, it is not

¹⁵ TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. Review date: June, 2013. Accessed June 20, 2015. http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidenceexpert/ND_PR/evidenceexpert/CS/

¹⁶ Hale's 2012 Medications and Mother's Milk. 15th Edition, Amarillo, TX.

¹⁷ LACTMED®: The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. LactMed Record Number: 990; Last Revision Date: 20130907

¹⁸ Efudex Cream labeling

possible to identify the drug dose or if the drug was applied during organogenesis. Additionally, determination of the likely causality of a cleft lip and palate following administration of any drug is hampered by the high prevalence of this malformation. Cleft lip and palate is one of the most common birth defects.

This reviewer was not able to locate the case report of an infant born with a ventricular septal defect following application of Efudex Cream to mucous membrane areas. Ventricular septal defects are one of the most common congenital cardiovascular malformations and determination of cause and effect following mucosal Efudex Cream application is difficult.

Lastly, the causality of a spontaneous abortion (noted as miscarriage in the Efudex Cream labeling) following intravaginal Efudex Cream application is dubious. The dose, timing and duration of use of topical fluorouracil are not reported. Spontaneous abortions are very common, occurring in 15% to 20% of all clinically recognized pregnancies.

The case report by Stephens *et al.*, above may be the infant with multiple birth defects referred to in the Efudex Cream labeling. As discussed, the administration of parenteral fluorouracil occurred after organogenesis making it unlikely that the defects reported were induced by fluorouracil.

No reports could be found in the published literature of birth defects following prenatal use of topical fluorouracil which are likely related to drug exposure during pregnancy. It is unknown if the cases of birth defects noted in the Efudex Cream labeling were generated from reports to the manufacturer or the Agency. The pharmacokinetic study described in subsection (12.3) of the Tolak Cream labeling indicates that the systemic fluorouracil exposure from topical application is exceedingly low. The labeling should also state that the data are insufficient to draw a clear conclusion on drug-associated risk. Emphasis in the labeling regarding a theoretical risk may cause undue concern, particularly for women with inadvertent exposure. Additionally, if there is indeed a serious risk of systemic exposure from Tolak Cream, its labeling should include information on the nine Warnings and Precautions (not including Embryofetal Toxicity) found in parenteral fluorouracil labeling. Therefore, DPMH finds the data demonstrate that the teratogenic risk from Tolak Cream is very low and they do not support a contraindication during pregnancy for Tolak Cream.

DPMH recommends DDDP consider a drug utilization review to assist in understanding the full scope of topical fluorouracil use in females of reproductive potential. Given the variety of other pharmaceutical treatments and non-pharmaceutical treatment modalities for an actinic keratosis lesion in a pregnant woman, DPMH also recommends addition of a comment in the Pregnancy subsection (8.1) of labeling encouraging non-pharmaceutical treatments.

Lactation Labeling

There are no data on the presence or absence of fluorouracil in breast milk. Data to assess the possible fluorouracil exposure via breastmilk includes the pharmacokinetics

study (labeling subsection 12.3) which determined the maternal C_{max} in plasma. In that study more than one third (n=8) of the 21 patients had no measureable level of fluorouracil in their plasma. For the remaining patients, their C_{max} was reached approximately one hour after topical application of Tolak Cream. This would indicate that there is a relatively short window during which fluorouracil will be present in the plasma to be able to be transferred to breastmilk.

The LactMed review of topically administered fluorouracil characterized the possible risk to the breastfed infant as negligible – if care is taken to prevent direct contact of the infant’s skin and the Tolak Cream treated area. DPMH recommends that a lactating woman undergoing treatment with topical fluorouracil should be able to choose whether she wishes to breastfeed her infant during treatment following a discussion of the risks and benefits of breastfeeding with her by her health care provider.

ADDITIONAL CONSIDERATIONS

DPMH participated in meetings with the DDDP review team from April through August, 2015. Meeting discussions focused on the labeling language for a contraindication for use in pregnant women and the level of warning of potential embryofetal harm. As outlined above, DPMH does not believe the evidence supports a contraindication for pregnant women in labeling. DDDP has decided to maintain the contraindication similar to Efudex Cream. DDDP remains concerned about the teratogenic potential from systemic exposure from Tolak Cream because 1) no lower threshold has been established as there are no nonclinical studies performed with topical fluorouracil; and, 2) the off-label intravaginal use. Because actinic keratosis commonly affects older adults, DDDP does not believe the contraindication will cause undue concern to the majority of patients using Tolak Cream.

DPMH and DDDP agree that there is opportunity for ongoing discussion regarding labeling language for safe use of Tolak Cream in pregnancy and a path forward for full conversion of all fluorouracil topical cream product labeling to the PLLR format. DDDP has determined that the Tolak Cream labeling will not conform to PLLR format at this time. The application was pending on the day PLLR became effective (June 30, 2015) and is required to comply with PLLR before June 30, 2019.

LABELING RECOMMENDATIONS

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,”¹⁹ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are

¹⁹ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

subject to the 2006 Physicians Labeling Rule²⁰ format to include information about the risks and benefits of using these products during pregnancy and lactation.

The following are the DPMH Maternal Health Team recommendations for the proposed labeling for Tolak Cream in PLLR format.

²⁰*Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

HIGHLIGHTS OF PRESCRIBING INFORMATION

Tolak (fluorouracil) Cream, 4%

For topical use only

Initial US Approval: 1962

HIGHLIGHTS

-----USE IN SPECIFIC POPULATIONS-----

FULL PRESCRIBING INFORMATION: CONTENTS*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

Animal Data

Animal reproduction studies have not been conducted with (b) (4) fluorouracil. Fluorouracil administered parenterally (b) (4) teratogenic in mice, rats, and hamsters when given at (b) (4) doses equivalent to the usual human intravenous dose. Fluorouracil exhibited maximum teratogenicity when given to mice as single intraperitoneal injections of 10 to 40 mg/kg on day 10 or 12 of gestation. Similarly, intraperitoneal doses of 12 to 37 mg/kg given to rats between days 9 and 12 of gestation and intramuscular doses of 3 to 9 mg/kg given to hamsters between days 8 and 11 of gestation were teratogenic and/or embryotoxic (i.e., resulted in increased resorptions or embryoletality). In monkeys, divided doses of 40 mg/kg given between days 20 and 24 of gestation were not teratogenic. However, doses higher than 40 mg/kg resulted in spontaneous abortions.

12.3 Pharmacokinetics

A systemic absorption study of topically applied Tolak Cream was performed in 21 patients with at least 3 actinic keratosis lesions (4 mm or greater in diameter). The steady state concentration of 5-fluorouracil in plasma was examined at 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours after the last dose of a 4-week regimen in subjects with actinic keratosis after “area application” to area(s) in which actinic keratosis lesions were identified at baseline. Areas were defined as the whole region of the left cheek, right cheek, chin and forehead, bald scalp, and right and left ears, where actinic keratosis was identified at baseline. Thus, for example, if an actinic keratosis lesion was identified on the left cheek, Tolak was to be applied as a thin film to the whole area of the left cheek.

Eight patients had undetectable levels of plasma 5-fluorouracil (the lower limit of quantification was 1.00 ng/ml) in all plasma samples following treatment with Tolak Cream. Among patients with detectable plasma 5-fluorouracil levels, the highest level of plasma 5-fluorouracil was generally observed at 1 hour post-dose. The mean observed maximum concentration (\pm standard deviation) of plasma 5-fluorouracil was 3.66 (\pm 1.58) ng/mL with the range between 1.11 – 7.35 ng/mL.

The catabolism of 5-fluorouracil results in inactive degradation products (such as CO₂, urea, α -fluoro- β -alanine).

17 PATIENT COUNSELING INFORMATION

APPENDIX

Currently Available Topical Fluorouracil Formulations

Drug	NDA or ANDA	Marketing Status	Manufacturer
<u>Carac</u>	NDA 20985	Prescription	Valeant Pharms North
Efudex	NDA 16831	Prescription	Valeant Pharms Intl
<u>Fluoroplex</u>	NDA 16988	Prescription	Elorac
Fluorouracil Topical	ANDA 77524	Prescription	Spear Pharms
Fluorouracil Topical	ANDA 90368	Prescription	Taro
Fluorouracil Topical	ANDA 203122	Prescription	Spear Pharms
Fluorouracil Topical	ANDA 77524	Prescription	Spear Pharms
Fluorouracil Topical	ANDA 76526	Prescription	Taro

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

/s/

CAROL H KASTEN
09/03/2015

TAMARA N JOHNSON
09/03/2015

LYNNE P YAO
09/04/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: August 4, 2015

To: Strother Dixon
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Tara Turner, Pharm.D., MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Pharm.D., BCPS, RAC, Acting Team Leader, OPDP

Subject: **NDA 022259**
Tolak (fluorouracil) Cream, 4% for topical use only

On January 27, 2015, DDDP consulted OPDP to review the draft Package Insert (PI), Patient Package Insert (PPI), and carton and container labeling for Tolak (fluorouracil) Cream, 4%, for topical use only (Tolak) for the NDA resubmission received on December 18, 2014.

OPDP reviewed the proposed substantially complete version of the PI provided by DDDP via e-mail on July 20, 2015. OPDP also reviewed the proposed carton and container labeling submitted to the electronic document room on February 26, 2015. The Division of Medical Policy Programs (DMPP) and OPDP provided comments on the PPI for Tolak under separate cover. OPDP's comments on the PI and carton and container labeling are provided below.

Thank you for your consult. If you have any questions about OPDP's comments, please contact Tara Turner at 6-2166 or at Tara.Turner@fda.hhs.gov.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

TARA P TURNER
08/04/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 30, 2015

To: Kendall Marcus, MD
Director
Division of Dermatology and Dental Products (DDDP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Tara Turner, PharmD, MPH
Regulatory Review Officer
Melinda Mclawhorn, PharmD, BCPS, RAC
Acting Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TOLAK (fluorouracil)

Dosage Form and Route: Cream, 4% For topical use only

Application Type/Number: 022259

Applicant: Hill Dermaceuticals, Inc.

1 INTRODUCTION

On December 18, 2014, Hill Dermaceuticals, Inc. submitted for the Agency's review a Class 2 resubmission of their Original 505(b)(2) New Drug Application (NDA) 022259 for TOLAK (fluorouracil) Cream, in response to the Agency's Complete Response letter dated June 22, 2009. The proposed indication for TOLAK (fluorouracil) Cream is for the topical treatment of actinic keratosis lesions of the face, ears, and/or scalp. The Reference Listed Drug is Efudex (fluorouracil), NDA 16831.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on January 27, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TOLAK (fluorouracil) Cream.

2 MATERIAL REVIEWED

- Draft TOLAK (fluorouracil) Cream PPI received on February 23, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 20, 2015.
- Draft TOLAK (fluorouracil) Cream Prescribing Information (PI) received on February 23, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 20, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
07/30/2015

MELINDA W MCLAWHORN
07/30/2015

BARBARA A FULLER
07/30/2015

LASHAWN M GRIFFITHS
07/30/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: March 26, 2015

Requesting Office or Division: Division of Dermatology and Dental Products (DDDP)

Application Type and Number: NDA 022259

Product Name and Strength: Tolak (fluorouracil) Cream, 4%

Product Type: Single-ingredient product

Rx or OTC: Rx

Applicant/Sponsor Name: Hill Dermaceuticals Inc.

Submission Date: February 26, 2015

OSE RCM #: 2015-193

DMEPA Primary Reviewer: Carlos M Mena-Grillasca, RPh

DMEPA Team Leader: Kendra Worthy, PharmD

1 REASON FOR REVIEW

As part of the evaluation for NDA 022259, DDDP requested DMEPA evaluate the proposed container labels, carton labeling, and Full Prescribing Information (FPI) for Tolak cream for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – n/a
ISMP Newsletters	D – n/a
FDA Adverse Event Reporting System (FAERS)*	E* - n/a
Other	F – n/a
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant is proposing 40 g tube package size. We note that other fluorouracil cream formulations marketed are available in 30 g and 40 g tubes. Therefore, we find the proposed package size adequate.

We note that by choosing to color block the proprietary name, it is not commensurate in prominence to the establish name as required by CFR 201.10(g)(2). In addition, the applicant has included partial information regarding the indication of use; i.e. "For the treatment of Actinic Keratosis", whereas the labeled indication is specific for the actinic keratosis lesions of the face, ears, and scalp". Also, the Rx Only statement is more prominent than more important information on the label (i.e. the route of administration statement).

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed packaging configuration is adequate. However, DMEPA recommends the following container labels and carton labeling comments be implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR (b) (4)

A. General Comments (40 g container label and carton labeling)

1. Revise the presentation of the proprietary name to remove the color blocking. As currently presented, it is not commensurate in prominence to the established name as required by CFR 201.10(g)(2).
2. Ensure the presentation of the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).
3. Remove the statement “(b) (4)”, as this is partial information that could lead to medication errors. In addition, remove the patent number as this is not required and clutters the labels.
4. Relocate the statement “Contains (b) (4) Peanut Oil” to the location where the indication and patent information were previously located and increase its prominence by increasing the font size and bolding.
5. Decrease the prominence of the “Rx Only” statement by unbolding.
6. Increase the prominence of the route of administration statement by increasing the font size and bolding so that it reads:

For Topical Use Only

Not for ophthalmic, oral or intravaginal use

7. Include the statement “Wash hands after each application.” after the dosage statement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tolak that Hill Dermaceuticals submitted on February 26, 2015.

Table 2. Relevant Product Information for Tolak	
Initial Approval Date	n/a
Active Ingredient	Fluorouracil
Indication	Topical treatment of actinic keratosis lesions of the face, ears, and scalp.
Route of Administration	Topical
Dosage Form	Cream
Strength	4%
Dose and Frequency	Apply once daily in an amount sufficient to cover the lesions of the face, ears, and/or scalp with a thin film, using the fingertips to gently massage the medication uniformly into the skin
How Supplied	40 g tubes
Storage	25°C (77°F); with excursions permitted to 15° – 30°C (59° – 86°F)
Container Closure	n/a

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March, we searched the L:drive and AIMS using the terms, Tolak, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 2 previous labeling reviews for Tolak that were performed during the first NDA review cycle. We note that the current labels and labeling under review differ from the original labels; therefore, the previous labeling reviews performed by DMEPA are not relevant.

APPENDIX C. HUMAN FACTORS STUDY

N/A

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F.

N/A

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/s/

CARLOS M MENA-GRILLASCA
03/26/2015

KENDRA C WORTHY
03/26/2015

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 022259

Application Type: New NDA (Resubmission)

Name of Drug/Dosage Form: Tolak (fluorouracil) cream, 4%

Applicant: Hill Dermaceuticals

Receipt Date: December 18, 2014

Goal Date: June 18, 2015

1. Regulatory History and Applicant's Main Proposals

The sponsor originally submitted a NEW NDA on August 17, 2007. The Division of Dermatology and Dental Products issued the sponsor a complete response letter on June 22, 2009. The sponsor resubmitted the NDA on December 18, 2014.

2. Review of the Prescribing Information

This review is based on the applicant's submitted pdf (March 2009 version) of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

The sponsor will be requested to submit the MS Word version to the NDA with the changes identified in the Appendix.

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 11, 2015. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
Comment:
- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.
Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
Comment: *The HL is greater than one-half page.*
- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment:
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
Comment:
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.
Comment:
- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
Comment: *The fifth bullet does not reference the section with a numerical identifier.*

Selected Requirements of Prescribing Information

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

NO 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment: The statement has a "THE" in the title.

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**"

The name of drug product should appear in UPPER CASE letters.

Comment: The drug name is not in upper case letters.

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

NO 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment: *The sponsor has included the title however since this a New NDA, there should not be any RMCs to add.*

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Selected Requirements of Prescribing Information

Dosage Forms and Strengths in Highlights

- N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *The product only has one dosage form.*

Contraindications in Highlights

- YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- NO 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *Add a "1" to the manufacturer's phone number. Remove the underline from the fda medwatch website.*

Patient Counseling Information Statement in Highlights

- NO 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment: *Add "and FDA-approved patient labeling" to the Patient Counseling Information Statement section.*

Revision Date in Highlights

- NO 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Change the date to MM/YYYY or to the PDUFA date of 06/2015.*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: *Subsection 5.3 has a spelling error (should be "Inflamed" instead of "Inflammed"). Subsection 6.1 should be "Clinical Trials Experience" instead of "Clinical Trial Adverse Reactions." Subsection 6.2 should be "Postmarketing Experience" instead of "Post-marketing Adverse Reactions." Subsection 13.1 Change "Carcinogenesis and Mutagenesis and Impairment of Fertility" to "Carcinogenesis, Mutagenesis, Impairment of Fertility." There is no subsection 13.2 in the FPI. Also, if there is a subsection 13.2 it should be titled "Animal Toxicology and/or Pharmacology."*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A 36. In the BW, all text should be **bolded**.

Comment:

- N/A 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- NO 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *The Patient Counseling section does not reference the Patient Information labeling.*

- NO** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *The patient labeling is a subsection of the Patient Counseling Information section.*

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

STROTHER D DIXON
02/02/2015

BARBARA J GOULD
02/03/2015



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: May 15, 2008

To: Susan Walker, M.D., Director
Division of Dermatology and Dental Products

Through: Jodi Duckhorn, M.A., Team Leader
Patient Labeling and Education Team
Division of Risk Management (DRISK)

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Patient Labeling and Education Team
Division of Risk Management (DRISK)

Subject: Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Tolak (fluorouracil) Cream, 4%

Application Type/Number: NDA 22-259

Applicant/sponsor: Hill Dermaceuticals, Incorporated

OSE RCM #: 2008-720

1 INTRODUCTION

Hill Dermaceuticals, Incorporated submitted a New Drug Application (NDA) for Tolak (fluorouracil) Cream 4%, on August 17, 2007. Tolak Cream is indicated for the topical treatment of actinic keratosis lesions of the face, ears and scalp. The labeling for this submission is in PLR format and includes a proposed Patient Package Insert (PPI) in section 17 Patient Counseling Information, in the Professional Information (PI).

The review division requested that the Patient Labeling and Education Team review the PPI as proposed by the sponsor and further revised by the review division. This review is written in response to that request.

2 MATERIAL REVIEWED

- Tolak Cream PPI submitted on September 10, 2007, and further revised by the review division on April 25, 2008
- Tolak Cream PI submitted on September 10, 2007, and further revised by the review division on April 25, 2008

3 DISCUSSION

The purpose of patient information (b) (4) is to enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 8.4, and a Flesch Reading Ease score of 58.1. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the sponsor are acceptable; however, our changes have improved upon the readability scores. Our revised PPI has a Flesch Kincaid grade level of 6.1 and Flesch Reading Ease score of 71.5.

In our review of the PPI, we have:

- simplified wording where possible,
- made it consistent with the Professional Information,
- rearranged information to be consistent with PLR format
- removed unnecessary or redundant information
- Although not required for Patient Information, we have put this PPI in the question-and-answer format specified in the Medication Guide Regulations (21 CFR 208.20) that we recommend for all FDA approved patient labeling.
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

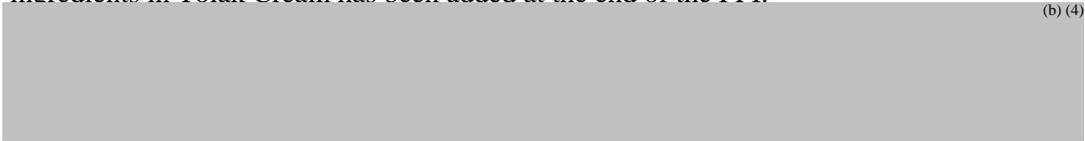
See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined and italicized.***

We are providing the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

4 CONCLUSIONS AND RECOMMENDATIONS

1. The Review Division should consult the Safety Requirements Team as soon as possible to determine if the product will need a Risk Evaluation and Mitigation Strategy (REMS).
2. The bullet for allergy was deleted from the section called “Who should not use Tolak Cream?” Allergy is not a contraindication to use. An allergy statement has been added to the new section “What should I tell my doctor before using Tolak Cream?” A list of ingredients in Tolak Cream has been added at the end of the PPI.

3.  (b) (4)

4. Under the section “What are the possible side effects of Tolak Cream?” the sponsor should list the signs and symptoms of allergic reaction that have been seen with Tolak Cream, and also the actions to be taken by the patient. This should be added to the PPI and PI section 17. The language in the PPI must be consistent with the language in the PI.
5. We have added the statement, “Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.” This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* in Federal Register Vol. 73, No. 2, p.402-404, 1/3/2008). Although not required for voluntary PPIs like Tolak Cream, we recommend adding this language to all FDA-approved patient labeling for consistency.

Please let us know if you have any questions.

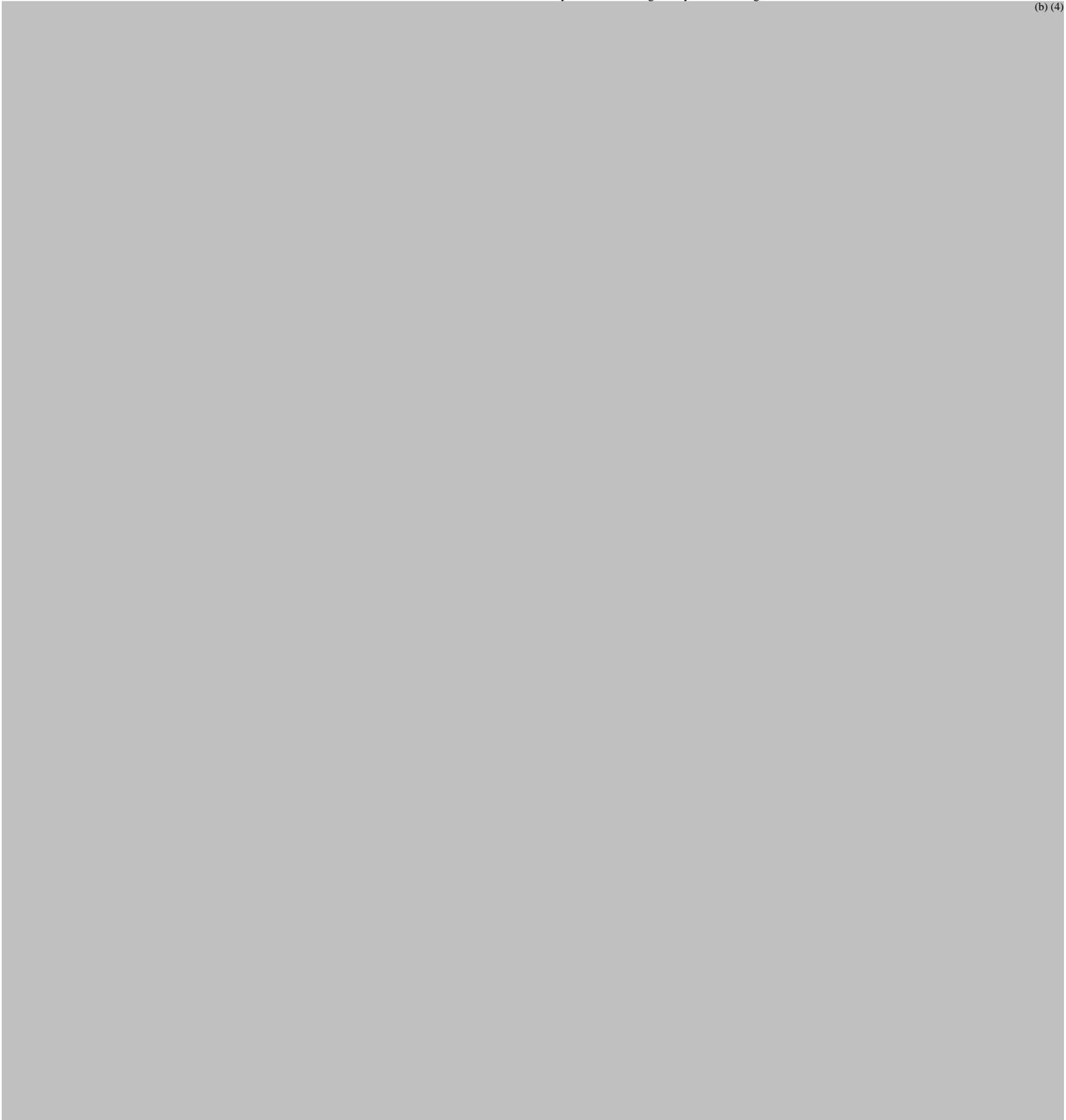
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/s/

Sharon Mills
5/15/2008 01:04:52 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
5/15/2008 01:38:22 PM
CSO



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/s/

Melissa Furness

4/17/2008 09:47:17 AM

CSO

Comments in this review were based upon the draft
label received from DDDP.

Laurie Burke

4/18/2008 04:22:23 PM

INTERDISCIPLINARY

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: April 14, 2008

TO: Catherine Carr, Regulatory Project Manager
David Kettl, M.D., Medical Officer
Division of Dermatologic and Dental Drug Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-259

APPLICANT: Hill Dermaceuticals, Inc.

DRUG: 5-Fluorouracil Cream, 4%

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Treatment of actinic keratoses

CONSULTATION REQUEST DATE: November 5, 2007

DIVISION ACTION GOAL DATE: June 20, 2008

PDUFA DATE: June 20, 2008

I. BACKGROUND:

5-Fluorouracil Cream, 4% is indicated for the topical treatment of multiple actinic keratoses (AK) of the face, scalp, and ears. The protocols inspected include:

#HD-FUP3B-048, entitled, “A Randomized, Evaluator Blinded, Vehicle-Controlled Multicenter Study Of The Safety And Efficacy Of 4% Tradename (Fluorouracil) Cream Versus Its Vehicle Cream Versus Efudex[®] Cream In The Treatment Of Actinic Keratosis”, and

#HD-FUP3S-049, entitled, “A Randomized, Double Blind, Vehicle-Controlled Multi-Center Study Of The Safety And Efficacy Of 4% Tradename (Fluorouracil) Cream Versus Its Vehicle Cream In The Treatment Of Actinic Keratosis

Study protocol no. HDFUP3B-048 was an investigator-blind, 4-arm, parallel group study. Efficacy of the product was compared with Efudex[®] (noninferiority) and to its vehicle (superiority) for a 4-week duration of treatment. Study protocol no. HD-FUP3S-049 was a double-blind, 2-arm, parallel group study. The product was compared with its vehicle in a superiority study for a 4-week duration of treatment. For both studies, the primary efficacy endpoint was the proportion of subjects with complete clearing of all AK lesions at 4 weeks of treatment, in the ITT population.

In study 048, site 022 was selected because it had the second largest enrollment (59 subjects) and one of the largest treatment effects.

In study 048, site 011 was one of the larger enrollers (48 subjects), but preliminary review of the data from this site suggested that the lesion count assessment did not follow the expected pattern. Typically, application of active drug causes increased erythema and there is an expected increase in the lesion count at intermediate assessment timepoints. This was not shown from the subjects enrolled at site 011, and the data showed no change from baseline to the midway point of the trial.

In study 049, site 003 was the second largest site with 24 subjects enrolled. Overall efficacy appeared to be lower in this second study, but no specific site drove the efficacy data.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor City, State, or Country	Protocol #:/ Site #:/ # of Subjects:/	Inspection Dates	Final Classification
Mark Ling, M.D. MedaPhase, Inc. 710 Newnan Crossing Bypass Newnan, GA 30263 Tele: 404-378-5545 Fax: 404-378-7931 mling@medaphase.com	HD-FUP3B-048/ 011/ 48 enrolled	22 Jan – 8 Feb 08	NAI
Eduardo Tschen, M.D. Academic Dermatology Associates 1203 Coal SE, Suite B Albuquerque, NM 87106 Tele: 505-247-4220 Fax: 505-247-0367 eatschen@aol.com	HD-FUP3B-048/ 022/ 59 enrolled/	7 Jan – 7 Feb 08	NAI
Kenneth Gross, M.D. Skin Surgery Medical Group, Inc. Clinical Research Department 5222 Balboa Avenue, 6th Floor San Diego, CA 92117 Tele: 858-292-5101	HD-FUP3B-049/ 003/ 24 enrolled/	7-12 Feb 08	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI-No Response Requested= Deviations(s) from regulations.

VAI-R = Response Requested = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 and/or communications with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Site 011

Mark Ling, M.D.
MedaPhase, Inc.
710 Newnan Crossing Bypass
Newnan, GA 30263
Tele: 404-378-5545
Fax: 404-378-7931
mling@medaphase.com

- a. **What was inspected:** Consent forms for all 48 subjects were reviewed. An in-depth audit of 16 of the subjects' records was conducted. The inspection covered, but was not limited to, lesion count practices, IRB approval, CRFs, inspection/exclusion criteria, blinding, adverse event reporting, drug accountability, and study monitoring.
- b. **General observations/commentary:** No regulatory violations were noted.

c. **Assessment of data integrity:** Data appear acceptable in support of the pending application.

2. Site 022

Eduardo Tschén, M.D.
Academic Dermatology Associates
1203 Coal SE, Suite B
Albuquerque, NM 87106
Tele: 505-247-4220
Fax: 505-247-0367
eatschen@aol.com

a. **What was inspected:** 59 subjects were enrolled and randomized to the study. All consent forms were reviewed as were test article accountability records. Source data and CRFs were reviewed for one-third of the subjects.

b. **General observations/commentary:** The investigator noted that when lesion counts exceeded 50 within a given area, it was documented as “Too Numerous To Count” (TNTC) though the protocol required that lesions be enumerated. This resulted in sponsor data listings noting numerical values for Treated Lesion Totals (resulting from the Last Observation Carried Forward (LOCF)) for Weeks 2, 3, and 4 when source documents recorded lesion counts as “TNTC” and CRFs recorded the counts as “Not Done”. Otherwise, the study appears to have been conducted in accordance with the protocol and no significant deviations/deficiencies were noted.

c. **Assessment of data integrity:** The above deviation is unlikely to have a significant impact upon data integrity. Data appear acceptable in support of the pending application.

3. Site 003

Kenneth Gross, M.D.
Skin Surgery Medical Group, Inc.
Clinical Research Department
5222 Balboa Avenue, 6th Floor
San Diego, CA 92117
Tele: 858-292-5101

a. **What was inspected:** Medical records, source documents, consent forms, and CRFs were reviewed for all 24 subjects enrolled at this site. Test article accountability records were also reviewed. Lesion counts at baseline and final evaluation were reviewed and compared with sponsor data listings.

- b. **General observations/commentary:** Five subjects did not meet all inclusion/exclusion criteria: subjects 001, 012, and 100 had prior cryotherapy within the treatment area within two months of study enrollment; subject 013 had a lesion within the treatment area suspected to be squamous cell carcinoma; and subject 016 had used another treatment (Aldara) for actinic keratosis just prior to study enrollment.
- c. **Assessment of data integrity:** The review division may wish to consider the exclusion of data from subjects 001, 012, 013, 016, and 100 noted above; otherwise, data appear acceptable in support of the pending application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Overall, the data generated by the sites of Drs. Ling, Tschen, and Gross appear acceptable in support of the pending application.

{See appended electronic signature page}

Roy Blay, Ph.D.
GCP Reviewer
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance

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this page is the manifestation of the electronic signature.**

/s/

Roy Blay
4/16/2008 01:11:57 PM
CSO

Constance Lewin
4/16/2008 02:51:06 PM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-259 Supplement # Efficacy Supplement Type SE- N/A

Proprietary Name: Tradename to be determined
Established Name: 5-Fluorouracil Cream
Strengths: 4%

Applicant: Hill Dermaceuticals, Inc.
Agent for Applicant (if applicable): N/A

Date of Application: August 17, 2007
Date of Receipt: August 20, 2007
Date clock started after UN: N/A
Date of Filing Meeting: October 9, 2007
Filing Date: October 19, 2007
Action Goal Date (optional): June 20, 2008 User Fee Goal Date: June 20, 2008

Indication(s) requested: Topical treatment of multiple actinic keratosis of the face, scalp, and ears

Type of Original NDA: (b)(1) (b)(2) X

Review Classification: S X P
Resubmission after withdrawal? X No Resubmission after refuse to file? X No
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.) No

Form 3397 (User Fee Cover Sheet) submitted: YES X NO

The form was not signed. RPM will request the applicant to submit a signed form.

User Fee Status: Paid X Exempt (orphan, government)
Waived (e.g., small business, public health)

• Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO X

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

• Does another drug have orphan drug exclusivity for the same indication? YES NO X

• If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A X YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

• Is the application affected by the Application Integrity Policy (AIP)? YES NO X

• Does the submission contain an accurate comprehensive index? YES X NO
If no, explain: **Although the index is accurate and comprehensive, it is poorly organized.**

• Was form 356h included with an authorized signature? YES X NO

- Submission complete as required under 21 CFR 314.50? YES X NO
If no, explain: **Electronic content of labeling not submitted per 314.50(l)(1)(i) with original submission, but submitted upon request. The SPL was requested in the 74-day letter.**
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).
 1. This application is a paper NDA YES X
 2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format X
Combined NDA and CTD formats
- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, X Years NO
- Correctly worded Debarment Certification included with authorized signature? YES X NO
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO X

The applicant requested a waiver of pediatric studies on October 15, 2007.

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? **Submitted on October 15, 2007.** YES X NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X
- Financial Disclosure forms included with authorized signature? YES X NO
- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO
- PDUFA and Action Goal dates correct in tracking system? YES X NO
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: **IND 69,841**
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) November 21, 2005 NO
- Pre-NDA Meeting(s)? Date(s) Meeting Cancelled.
Minutes/Comments to sponsor's
questions dated and faxed on April 25,
2007 NO

- Any SPA agreements? Date(s) **1st SPA granted. Response letter dated 2-16-06. 2nd SPA requested, but denied. Denial letter dated 3-5-07.** NO

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO X
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES X NO
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO
Recommend DDMAC consult for labeling.
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
Sponsor will submit trade name by October 31, 2007.
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES X NO
Recommend DSRCS consult for PPI.
- Risk Management Plan consulted to OSE/IO? N/A X YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A X YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If a parenteral product, consulted to Microbiology Team? N/A X YES NO X

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 9, 2007

NDA #: 22-259

DRUG NAMES: 5-Fluorouracil Cream, 4%

APPLICANT: Hill Dermaceuticals

BACKGROUND: This application was submitted pursuant to section 505(b)(2) for 4% 5-fluorouracil cream in peanut oil vehicle for the topical treatment of multiple actinic keratosis of the face, scalp, and ears. The RLD indicated in the application is Efudex Cream, 5%.

ATTENDEES: Catherine Carr, Stanka Kukich, Markham Luke, Dave Kettl, Jane Liedtra, Paul Brown, Barbara Hill, Kathleen Fritsch, Shulin Ding, Jane Chang, and Sue Chih Lee.

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Dave Kettl
Secondary Medical:	Markham Luke
Statistical:	Kathleen Fritsch
Pharmacology:	Barbara Hill
Chemistry:	Shulin Ding
Biopharmaceutical:	Tapash Ghosh
Regulatory Project Management:	Catherine Carr
DSI:	
OPS:	

Other Consults:

Per reviewers, are all parts in English or English translation? YES X NO

CLINICAL FILE X REFUSE TO FILE

• Clinical site audit(s) needed? YES X NO

If no, explain:

• Advisory Committee Meeting needed? YES, date if known _____ NO X

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A X YES NO

CLINICAL MICROBIOLOGY N/A X FILE REFUSE TO FILE

STATISTICS N/A FILE X REFUSE TO FILE

BIOPHARMACEUTICS		FILE	X	REFUSE TO FILE	<input type="checkbox"/>	
• Biopharm. study site audits(s) needed?		YES	<input type="checkbox"/>	NO	X	
PHARMACOLOGY/TOX	N/A	<input type="checkbox"/>	FILE	X	REFUSE TO FILE	<input type="checkbox"/>
• GLP audit needed?		YES	<input type="checkbox"/>	NO	X	
CHEMISTRY		FILE	X	REFUSE TO FILE	<input type="checkbox"/>	
• Establishment(s) ready for inspection?		YES	X	NO	<input type="checkbox"/>	
During the October 18, 2007 teleconference, sponsor indicated that they were ready for establishment inspection.						
• Sterile product?		YES	<input type="checkbox"/>	NO	X	
If yes, was microbiology consulted for validation of sterilization?		YES	<input type="checkbox"/>	NO	X	

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - X Filing issues to be communicated by Day 74.

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
3. Convey document filing issues/no filing issues to applicant by Day 74.

Catherine Carr
Regulatory Project Manager

Appendix B to NDA Regulatory Filing Review

Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES X NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): **NDA 16-831, Efudex (5-FU Cream, 5%)**

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO X

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO X

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO X

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

6. (a) Is there a pharmaceutical alternative(s) already approved? YES X NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES X NO

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES X NO

If “Yes,” to (c), proceed to question 7.

NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s): NDA 20-985/CARAC Cream, 0.5%/Sanofi Aventis (patent expires 6/2/2021)
NDA 16-831/EFUDEX Cream, 5%/Valeant Pharm
NDA 16-988/Fluoroplex Cream, 1%/Allergen Herbert

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES X NO

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

Yes, the literature cites Efudex Cream.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”). **This application provides for a change in strength.**

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO X

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO X

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product’s active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES NO X

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO X

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.). **Upon submission, the application did not contain a patent certification for the RLD. Sponsor submitted it in an amendment, dated October 15, 2007.**

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):
NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES X NO

*If "Yes," what is the listed drug product(s) **EFUDEX** and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug? 1) PHARM/TOX - relies on literature of active ingredient.*

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES X NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If “Yes,” please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Catherine Carr
4/4/2008 09:42:35 AM
CSO

Maria Walsh
4/4/2008 10:26:24 AM
CSO
for Margo Owens