# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 022259Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

## OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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| NDA: 22259 | Submission Date(s): 12/17/2014 |
| Brand Name | Tolak cream, 4% |
| Generic Name | Fluorouracil |
| Primary Reviewer | Doanh Tran, Ph.D. |
| Secondary Reviewer | Capt. E. Dennis Bashaw, Pharm.D. |
| OCP Division | Division of Clinical Pharmacology 3 |
| OND division | Division of Dermatology and Dental Products |
| Applicant | Hill Dermaceuticals, Inc. |
| Submission Type | Resubmission/Complete response |
| Formulation; Strength(s) | Cream, 4% |
| Indication | Treatment of actinic keratosis lesions of the face, ears, and scalp |

**Background:**
NDA 22259 was originally submitted on 8/17/2007. The Clinical Pharmacology review was conducted by Dr. Tapash Gosh and completed on 4/18/2008 with an acceptable recommendation. The NDA was issued a Complete Response letter on 6/22/2009 due to product quality deficiencies. Labeling review was suspended during the original NDA review cycle.

**Current submission:**
In this submission the applicant has provided their complete response to the quality deficiencies. In addition, the sponsor also submitted final study report for long term safety study HD-FUP4LTS-050. A clinical pharmacology review of these data is not needed. This review will address the proposed label for Tolak cream, 4%.

**Labeling recommendation:**
The labeling recommendations are based on the clinical pharmacology review by Dr. Tapash Ghosh dated 4/18/2008. It appears that the labeling recommendations from Dr. Ghosh were communicated to the applicant during the original review cycle. The sponsor's proposed label sections 7 and 12.3 are generally consistent with Dr. Ghosh's recommendations. This reviewer agrees with the applicant proposal in section 7 and 12.3 with minor edits as noted below.

*Recommended additions are noted as double underline and deletions are noted as strikethrough.*

**7 DRUG INTERACTIONS**

Subjects using systemic steroids, immunosuppressants, and immunomodulators were generally excluded from the clinical studies of Tolak Cream, as were subjects who used retinoids, topical steroids, glycolic acid products, alpha-hydroxy products, and chemical peeling products in the treatment areas. No clinical trials were designed to specifically evaluate drug interactions.

**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 (± standard deviation) of plasma 5-fluorouracil was 3.66 (±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 $CO_2$, urea, α-fluoro-β-alanine).

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DOANH C TRAN
07/16/2015

EDWARD D BASHAW
07/16/2015

# Clinical Pharmacology Review

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|---|---|
| NDA: | 22-259 |
| SUBMISSION DATES: | August 17, 2007 and September 10, 2007 |
| SUBMISSION TYPE | Original NDA |
| PRODUCT (Generic Name): | 5-Fluorouracil 4% |
| PRODUCT (Trade Name): | TOLAK |
| DOSAGE FORM: | Topical Cream |
| PROPOSED INDICATIONS: | Actinic keratosis |
| SPONSOR: | Hill Dermaceuticals |
| OCP DIVISION: | DCP 3 |
| REVIEWER: | Tapash K. Ghosh, Ph.D. |
| TEAM LEADER: | Lydia Velazquez, Pharm.D. |

## 1. EXECUTIVE SUMMARY

The sponsor has submitted a 505 (b)(2) new drug application (NDA) for 4% TOLAK 5-fluorouracil (5-FU) cream, a new formulation of 4% 5-FU cream in a peanut oil (b) (4) vehicle for the treatment of multiple actinic keratoses (AK) of the face, scalp and ears. Fluorouracil has been used clinically since 1957 both systemically and topically in the treatment of a variety of cancers (gastrointestinal, breast, ovarian, cervical, bladder, and skin cancers). 5-fluorouracil (5-FU) has been approved for topical (dermal) use in the treatment of AK since 1970 and is currently available in the following formulations:

| Concentration | Vehicle Type | Brand Name |
|---|---|---|
| 0.5% Fluorouracil | cream | Carac® |
| 1% Fluorouracil | cream | Fluoroplex® |
| 2% Fluorouracil | solution | Efudex® |
| 2% Fluorouracil | solution | Generic |
| 5% Fluorouracil | solution | Efudex® |
| 5% Fluorouracil | cream | Efudex® |

There are currently no approved 5-fluorouracil (5-FU) products at the 4% concentration, though other products are marketed with concentrations which vary from 0.5% once daily to 5% twice daily.

In the clinical development program, the sponsor conducted two Phase 3 efficacy and safety studies (HD-FUP3B-048 and HD-FUP3S-049), one Phase 2 dose-ranging study (HD-FUDR-045) and one Phase 2 pharmacokinetic (PK) and safety study (HD-FU1206SA). The PK study has been reviewed in detail in this review.

The objective of the PK study (HD-FU1206SA) was to compare the steady-state plasma concentration profile from the new topical cream developed by the sponsor versus Efudex® cream, an approved and currently marketed product in patients with AK. Systemic absorption of fluorouracil did not exceed the reference product following treatment of subjects with the proposed product once daily for up to 28 days compared to treatment with Efudex® twice daily for up to 28 days.

Based on the clinical review of the NDA, Tolak (fluorouracil) Cream 4% was superior to its vehicle in the treatment of actinic keratoses in two studies, 048 and 049, and this finding is the basis of demonstrating efficacy in this 505 (b)(2) application.

### 1.1 Recommendation:

The Office of Clinical Pharmacology has reviewed NDA 22-259 dated August 17, 2007 and finds the submission acceptable as systemic exposure of fluorouracil from TOLAK applied once daily for up to 28 days in subjects with AK was consistently low and did not exceed the systemic exposure of fluorouracil following application of Efudex® for up to 28 days per approved labeling.

**1.2 Labeling Recommendation:**

The Office of Clinical Pharmacology has the following recommendations for the proposed label to be addressed:

The following labeling recommendations in the "**Drug Interactions**" and "**Pharmacokinetics**" section of the proposed label should be addressed by the sponsor.

~~ABC~~ (Strikeout) suggests deletion of text and ***ABC*** (Bold, italics and underline) suggests insertion of new text.

**Drug Interactions**

(b) (4) Subjects using systemic steroids, immunosuppressants and immunomodulators were generally excluded from the clinical studies of TOLAK, as were subjects who used retinoids, topical steroids, glycolic acid products, alpha-hydroxy products, and chemical peeling products in the treatment areas. No clinical trials were designed to specifically evaluate drug interaction (b) (4)

**Pharmacokinetics**

A systemic absorption study of topically applied TOLAK was performed in 21 patients with ***a clinical diagnosis of ≥ 3 previously untreated actinic keratosis lesions of the face, and/or ears and/or scalp that were greater than or equal to 4 mm in the longest diameter***. (b) (4). 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.*** Among patients with detectable plasma 5-fluorouracil levels (b) (4) the highest level of plasma 5-fluorouracil was generally observed at 1 hour post-dose. ***For subjects who did have quantifiable levels of plasma fluorouracil, the time points at which these levels***

***were detected were between the 1 - 4 hour post-dose time points. No subject had detectable levels of plasma fluorouracil after 10 hours.*** The mean observed maximum concentration (± standard deviation) of plasma 5-fluorouracil was 3.66 (±1.58) ng/mL ***with a range of 1.11 – 7.35 ng/mL. The systemic absorption of Tolak is no greater than 5% 5-fluorouracil administered twice daily.***

The catabolism of 5-fluorouracil results in inactive degradation products (such as $CO_2$, urea, α-fluoro-β-alanine).

Please convey the above labeling changes and comments to the sponsor

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Primary Reviewer: Tapash K. Ghosh, Ph.D.
Division of Clinical Pharmacology 3

Team Leader: Lydia Velazquez, Pharm. D.
Div. of Clinical Pharmacology 3

CC list: HFD-540: NDA 22-259; CDER Central Document Room

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**1.3 Phase IV commitments:** None

**1.4 Summary of Important Clinical Pharmacology Findings**

The sponsor has submitted a 505 (b)(2) new drug application (NDA) for 4% TOLAK 5-fluorouracil (5-FU) cream, a new formulation of 4% 5-FU cream in a peanut oil (b) (4) vehicle for the treatment of multiple actinic keratoses (AK) of the face, scalp and ears. Fluorouracil has been used clinically since 1957 both systemically and topically in the treatment of a variety of cancers (gastrointestinal, breast, ovarian, cervical, bladder, and skin cancers). 5-fluorouracil (5-FU) has been approved for topical (dermal) use in the treatment of AK since 1970. There are currently no approved 5-fluorouracil (5-FU) products at the 4% concentration, though other products are marketed with concentrations which vary from 0.5% once daily to 5% twice daily.

In the clinical development program, the sponsor conducted two Phase 3 efficacy and safety studies (HD-FUP3B-048 and HD-FUP3S-049), one Phase 2 dose-ranging study (HD-FUDR-045) and one Phase 2 pharmacokinetic (PK) and safety study (HD-FU1206SA). The PK study has been reviewed in detail in this review.

The objective of the PK study (HD-FU1206SA) was to compare the steady-state plasma concentration profile from the new topical cream developed by the sponsor versus Efudex® cream, an approved and currently marketed product in patients with AK. Based on the limited data available, systemic exposure of fluorouracil from TOLAK applied once daily for up to 28 days in subjects with AK did not exceed compared to systemic exposure of fluorouracil following twice daily applications with the reference product Efudex® for up to 28 days. The data demonstrates that $C_{max}$ after once daily 4% TOLAK application was lower compared to twice daily Efudex® applications, what was expected as almost half of the fluorouracil was applied from the once daily proposed product compared to twice daily reference product, Efudex® Therefore, systemic safety of fluorouracil from TOLAK following once daily application should not be worse than already marketed twice daily Efudex® applications.

According to clinical review, Tolak (fluorouracil) Cream 4% was superior to its vehicle in the treatment of actinic keratoses in the two studies, 048 and 049, and this finding is the basis of demonstrating efficacy in this 505 (b)(2) application.

**2. QBR**

**2.1. General Attributes**

**2.1.1.** ***What are the chemical and physical-chemical properties of the drug substance?***

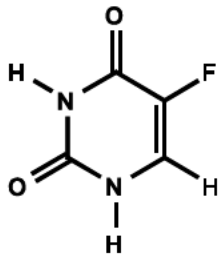
*Trade name*: TOLAK

*Generic name*: 5-Fluorouracil 4% Cream

*Chemical name:* 5-fluoro-2,4 (1H,3H)-pyrimidinedione

*Molecular formula/molecular weight:* $C_4H_3FN_2O_2$/130.1

*Chemical Structure*:




**Dosage Form Description**

TOLAK is a new formulation of 4% 5-fluorouracil (5-FU) in a cream vehicle for the treatment of AK. The vehicle itself is new; but all the excipients have been approved for use in other products.

A complete description of the quantitative composition of the finished product is provided in the following Table.

**Composition of 4% Fluorouracil Cream**

| **Component** | **Quantity per Batch** (b) (4) | |
|---|---|---|
| | **%** | **Kilograms** |
| 5-Fluorouracil USP | 4.0 | (b) (4) |
| Purified Water USP | (b) (4) | |
| (b) (4) Peanut Oil, NF | | |
| Isopropyl Myristate NF | | |
| Methyl Gluceth-10 | | |
| Arlacel-165 | | |
| Glycerin USP | | |
| Cetyl Alcohol NF | | |
| Stearyl Alcohol NF | | |
| Sodium Hydroxide NF | | |
| Stearic Acid NF | | |
| Butylated Hydroxytoluene NF | | |
| Methylparaben NF | | |
| Citric Acid USP | | |
| Propylparaben NF | | |
| **Total:** | | |

(b) (4) peanut oil, NF, at a concentration of (b) (4)% is used in a marketed drug product (Derma-smoothe; NDA 19-452). The sponsor stated that the (b) (4) peanut oil (b) (4) Each lot of raw material received by the sponsor undergoes ELISA test for peanut protein. While it appears that adequate safeguards to reduce the peanut allergens to acceptable levels are being implemented by the sponsor, it should be noted that the current Derma-Smoothe label still caries a precaution statement regarding use in peanut sensitive individuals.

### 2.1.2. *What is the proposed mechanism of drug action and therapeutic indication?*

5-fluorouracil (5-FU) is a pyrimidine analogue that works against AK lesions by competitively inhibiting the enzme thymidylate synthase, thereby creating a thymine deficiency and resulting in inhibition of DNA synthesis and cytotoxicity. Further cytotoxicity of 5-FU may come from incorporation of its metabolites into DNA and RNA.

### 2.1.3. *How was the dose/duration selected for 4% Fluorouracil Cream?*

The dose/duration of the proposed 4% TOLAK (Fluorouracil) cream was selected based on a Phase 2 dose-ranging study entitled "A Randomized, Evaluator Blinded, Vehicle Controlled, Parallel Group, Dose Ranging Study of the Safety and Efficacy of 4% TOLAK (5-Fluorouracil) Cream Versus its Vehicle Cream Versus Efudex® in the Treatment of Actinic Keratosis" (HD-FUDR-045). This was a multi-center, randomized, evaluator-blinded, parallel-group, dose-ranging, phase 2 trial in males and females with 5 to 20 clinically recognizable AK lesions of the face, and/or ears, and/or scalp. The study had the following active arms:

- 4% TOLAK, topical application applied once daily for four weeks
- 4% TOLAK, topical application applied twice daily for four weeks
- 4% TOLAK, topical application applied once daily for two weeks
- 4% TOLAK, topical application applied twice daily for two weeks

The reference arms were:

- Vehicle Cream, topical application applied twice daily for four weeks
- Efudex® 5% Cream, topical application applied twice daily for four weeks

Subjects applied the assigned study medication to the face, and/or ears, and/or scalp for two or four weeks as directed at the same time each day.

Criteria for Evaluation were as follows:

- The primary efficacy parameter was the proportion of patients in whom 100% of the lesions cleared at 4- weeks off study medication.
- Secondary efficacy parameters include the proportion of patients in whom 75% of the lesions have cleared at 4-weeks off-treatment and the percent change in number of AK lesions from baseline assessed at 4-weeks off-treatment.

The Efficacy Results as presented by the sponsor are as follows:

The greatest proportion of subjects with 100% clearance in the intent-to-treat population was reported in the 4% TOLAK once daily 4-weeks treatment group in which 80% of subjects (16/20) had 100% clearance. The 4% TOLAK twice daily 4-weeks and Efudex® twice daily 4-weeks treatment groups reported 75% of subjects with 100% clearance (15/20 subjects in each treatment group) followed by 60% of subjects in the 4% TOLAK once daily 2-weeks treatment group (12/20 subjects), 52% of subjects in the 4% TOLAK twice daily 2-weeks treatment group (11/21 subjects), and 15% of subjects in the vehicle twice daily 4-weeks treatment group (3/20 subjects).

The secondary endpoint was the proportion of subjects with 75% clearing of their actinic keratosis lesions at 4-weeks off-treatment. The greatest proportion of subjects with 75% clearance in the intent-to-treat population was reported in the 4% TOLAK once daily 4-weeks treatment group in which 100% of subjects (20/20) had 75% clearance. The 4% TOLAK twice daily 4-weeks and Efudex® twice daily 4-weeks treatment groups reported 95% of subjects with 75% clearance (19/20 subjects in each treatment group) followed by 85% of subjects in the 4% TOLAK once daily 2-weeks treatment group (17/20 subjects), 81% of subjects in the 4% TOLAK twice daily 2-weeks treatment group (17/21 subjects), and 20% of subjects in the vehicle twice daily 4-weeks treatment group (4/20 subjects).

***FDA Reviewer Comments:***

*The sponsor selected 4% TOLAK, topical application once daily for four weeks as the dose/duration for clinical trials based on the above results. However, there were only 20 patients in each parallel arm and there was a great deal of variability in the results. Therefore, the argument for choosing the proposed dose/dosing regiment is not very strong. Also, the reason for choosing "4%" as the proposed strength was not supported, but it is less than the currently approved Efudex 5% cream.*

## 2.2. Clinical Pharmacology

### 2.2.1 Pharmacokinetics

A systemic absorption study of topically applied TOLAK was performed in 21 patients with a clinical diagnosis of ≥ 3 previously untreated AK lesions of the face, and/or ears and/or scalp that were greater than or equal to 4 mm in the longest 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. Among patients with detectable plasma 5-fluorouracil levels (13 of 21), the highest level of plasma 5-fluorouracil was generally observed at 1 hour post-dose. For subjects who did have quantifiable levels of plasma fluorouracil, the time points at which these levels were detected were between the 1 - 4 hour post-dose time points. No subject had detectable levels of plasma fluorouracil after 10 hours. The mean observed maximum concentration (± standard deviation) of plasma 5-fluorouracil was 3.66 (±1.58) ng/mL with a range of 1.11 – 7.35 ng/mL. The systemic absorption of Tolak is no greater than 5% 5-fluorouracil administered twice daily.

### 2.2.2 Drug Interactions

Subjects using systemic steroids, immunosuppressants and immunomodulators were generally excluded from the clinical studies of TOLAK, as were subjects who used retinoids, topical steroids, glycolic acid products, alpha-hydroxy products, and chemical peeling products in the treatment areas. Although not currently required by the Agency, no clinical trials/pharmacokinetic trials were designed/conducted to evaluate drug interactions with the concomitantly applied topical formulations.

## 2.3. Analytical

*Were the correct moieties identified and properly measured?*

Yes. Plasma samples were extracted and analyzed for fluorouracil concentration according to a validated assay using LC/tandem MS with (b) (4). The assay parameters are listed in the following Table:

| | | |
|---|---|---|
| Species | Human | |
| Matrix | Plasma | |
| 5-FU Range | 1.00 to 500 ng/mL | |
| Analysis | LC/tandem MS with (b) (4) | |
| Sensitivity | Intra-assay | Inter-assay |
| | At least 66% of the individual replicates and the mean conc. deviates ≤ 12.0% from target; CV ≤ 15.0% | Overall mean conc. deviates ≤ 12.0% from target; CV ≤ 15.0% |

## 4. Appendix

### 4.1 Individual Clinical Studies

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**NDA: 22-259/Study HDFU1206SA** **Study Dates: Feb, 07 – Jul, 07**

**A Comparative Pharmacokinetic Evaluation of 4% TOLAK (Fluorouracil) Cream versus Efudex® Cream in Patients with Actinic Keratosis**

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**Objectives:** The objective of this study was to compare the steady-state plasma concentration profile of 4% TOLAK, a new 5-Fluorouracil (FU) 4% topical cream developed by Hill Dermaceuticals, Inc. (HD) versus Efudex® cream, an approved and currently marketed product, in patients with actinic keratosis (AK).

**Methodology:** This was an open-label, 28-day, multiple-dose, parallel-group, steady state, multicenter investigation with two treatment groups:

- 4% TOLAK cream applied once daily for 28 days (Batch # K050158. The batch was formulated using the to-be-marketed formulation)
- Efudex® 5% cream applied twice daily for 28 days (Batch # C0707/C0898)

A total of 88 subjects were screened based upon medical history, clinical laboratory results, physical exam, vital sign assessments and a clinical diagnosis of ≥ 3 previously untreated AK lesions of the face, and/or ears and/or scalp that were greater than or equal to 4 mm in the longest diameter. At 3 sites, 43 eligible subjects were enrolled and randomized to receive study medication. Thirty-nine (90.7%) subjects completed the study and 4 (9.3%) subjects terminated early, prior to completing the PK portion of the study.

4% TOLAK cream was applied once daily, with approximately 1.0 gram applied in the morning (approximately 8:00 AM). Efudex® cream was applied twice daily, with approximately 2.0 grams total (approximately 1.0 gram per application at 12-hour intervals; *e.g.* 8:00 AM and 8:00 PM). Subjects applied the assigned study medication to the areas of the face, and/or ears and/or scalp as directed, for 28 days using "area application". Area application was defined as application of the study medication to the whole region of the left cheek, right cheek, chin and forehead, bald scalp, and right and left ears, where AK was identified at baseline. That is, where an AK lesion was identified on the left cheek, the study medication was applied as a thin film to the whole area of the left cheek.

There was one Screening Visit and 4 in-clinic visits. During the baseline visit (Visit 2) a baseline blood sample was collected for pharmacokinetic (PK) analysis, followed by the first in-clinic application of study medication. Subjects returned to the clinic at Days 7

and 14 for collection of diaries, and adverse event (AE) information and concomitant medication assessments. Subjects returned to the clinic on Days 28-29 for a final in-clinic application of study medication followed by collection of serial blood samples at time 0 (pre-dose) and at 1, 2, 4, 6, 8, 10, 12, 16 and 24 hours after the final dose of study medication. Blood pressure and pulse rate were measured prior to discharge on Day 29.

A total of 43 adult male (n=29) and female (n=14) subjects with a diagnosis of AK from 44-81 years of age were enrolled and randomized to receive their assigned study medication. The race distribution was predominantly Caucasian (n=42, 97.7%). The mean age, weight, height, body mass index (BMI) and screening vital sign measurements were generally comparable among the two treatment groups.

All subjects who were enrolled and applied at least one dose of study medication were considered the Safety / Intent-to-Treat (ITT) population and were included in the demographic and safety analyses. The PK population included any subject with at least one plasma sample with quantifiable levels of fluorouracil.

Twenty-one (48.8%) subjects were assigned to the 4% TOLAK treatment group and 22 (51.2%) subjects were assigned the Efudex® treatment group. A total of 39 (90.7%) subjects completed the study, as defined by participation in the PK portion of the study (20 and 19 subjects in the 4% TOLAK and Efudex® treatment groups, respectively, completed) and 4 (9.3%) subjects did not participate in the PK portion of the study (1 subject in the 4% TOLAK treatment group and 3 subjects in the Efudex® treatment group) and therefore did not complete the study. Nine (20.9%) subjects [Five (23.8%) of 21 subjects in the 4% TOLAK treatment group and 4 (18.2%) of 22 subjects in the Efudex® ] discontinued study medication application due to an AE prior to the 28 ± 3 days administration period, although most of these subjects completed the PK portion of the study following their last at-home dose of study medication, as described in the protocol.

**Assay of Biological Samples:** Samples were extracted and analyzed for fluorouracil concentration according to a validated assay using LC/tandem MS with (b) (4). The assay parameters are listed in the following Table:

| | | |
|---|---|---|
| Species | Human | |
| Matrix | Plasma | |
| 5-FU Range | 1.00 to 500 ng/mL | |
| Analysis | LC/tandem MS with (b) (4) | |
| Sensitivity | Intra-assay | Inter-assay |
| | At least 66% of the individual replicates and the mean conc. deviates ≤ 12.0% from target; CV ≤ 15.0% | Overall mean conc. deviates ≤ 12.0% from target; CV ≤ 15.0% |

**Pharmacokinetic Results**: Most plasma samples at the majority of post-dose time points did not have detectable levels of fluorouracil. A plasma concentration-time profile could not be generated for any subject in either treatment group as values reported for the majority of time points sampled were below the lower limit of quantification (LLOQ) of 1.00 ng/ml.

Tables 1 and 2 summarize the number of sample time points with measurable levels of plasma fluorouracil by treatment group for the ITT and PK populations, respectively, and Tables 3 and 4 display $C_{max}$ and $T_{max}$ for all subjects in the ITT and PK populations, respectively, with measurable levels of plasma fluorouracil.

**Table 1: Measurable levels of plasma fluorouracil for ITT populations**

Summary of Pharmacokinetic Data
ITT Population

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| | Tradename (N=21) | | | Efudex® (N=22) | | |
| Time Point | Number of Samples Analyzed | Below LLOQ | Above LLOQ | Number of Samples Analyzed | Below LLOQ | Above LLOQ |
| Baseline | 21 | 21 ( 100%) | 0 (0.0 %) | 21 | 21 ( 100%) | 0 (0.0 %) |
| 0h (Pre Dose) | 20 | 20 ( 100%) | 0 (0.0 %) | 18 | 18 ( 100%) | 0 (0.0 %) |
| 1h Post dose | 20 | 7 (35.0%) | 13 (65.0%) | 19 | 8 (42.1%) | 11 (57.9%) |
| 2h Post dose | 20 | 11 (55.0%) | 9 (45.0%) | 19 | 10 (52.6%) | 9 (47.4%) |
| 4h Post dose | 19 | 9 (47.4%) | 10 (52.6%) | 18 | 11 (61.1%) | 7 (38.9%) |
| 6h Post dose | 20 | 14 (70.0%) | 6 (30.0%) | 19 | 14 (73.7%) | 5 (26.3%) |
| 8h Post dose | 20 | 19 (95.0%) | 1 ( 5.0%) | 19 | 17 (89.5%) | 2 (10.5%) |
| 10h Post dose | 20 | 19 (95.0%) | 1 ( 5.0%) | 19 | 19 ( 100%) | 0 (0.0 %) |
| 12h Post dose | 20 | 20 ( 100%) | 0 (0.0 %) | 19 | 19 ( 100%) | 0 (0.0 %) |
| 16h Post dose | 20 | 20 ( 100%) | 0 (0.0 %) | 19 | 19 ( 100%) | 0 (0.0 %) |
| 24h Post dose | 20 | 20 ( 100%) | 0 (0.0 %) | 19 | 19 ( 100%) | 0 (0.0 %) |

**Table 2: Measurable levels of plasma fluorouracil for PK Populations**

Summary of Pharmacokinetic Data
PK Analysis Population

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| | Tradename (N=21) | | | Efudex® (N=22) | | |
| Time Point | Number of Samples Analyzed | Below LLOQ | Above LLOQ | Number of Samples Analyzed | Below LLOQ | Above LLOQ |
| Baseline | 20 | 20 ( 100%) | 0 (0.0 %) | 18 | 18 ( 100%) | 0 (0.0 %) |
| 0h (Pre Dose) | 19 | 19 ( 100%) | 0 (0.0 %) | 15 | 15 ( 100%) | 0 (0.0 %) |
| 1h Post dose | 19 | 6 (31.6%) | 13 (68.4%) | 16 | 6 (37.5%) | 10 (62.5%) |
| 2h Post dose | 19 | 10 (52.6%) | 9 (47.4%) | 16 | 7 (43.8%) | 9 (56.3%) |
| 4h Post dose | 18 | 8 (44.4%) | 10 (55.6%) | 15 | 9 (60.0%) | 6 (40.0%) |
| 6h Post dose | 19 | 13 (68.4%) | 6 (31.6%) | 16 | 11 (68.8%) | 5 (31.3%) |
| 8h Post dose | 19 | 18 (94.7%) | 1 ( 5.3%) | 16 | 14 (87.5%) | 2 (12.5%) |
| 10h Post dose | 19 | 18 (94.7%) | 1 ( 5.3%) | 16 | 16 ( 100%) | 0 (0.0 %) |
| 12h Post dose | 19 | 19 ( 100%) | 0 (0.0 %) | 16 | 16 ( 100%) | 0 (0.0 %) |
| 16h Post dose | 19 | 19 ( 100%) | 0 (0.0 %) | 16 | 16 ( 100%) | 0 (0.0 %) |
| 24h Post dose | 19 | 19 ( 100%) | 0 (0.0 %) | 16 | 16 ( 100%) | 0 (0.0 %) |

**Table 3: $C_{max}$ and $T_{max}$ for all subjects in the ITT populations**

Table 14.2.2
Summary Statistics of Pharmacokinetic Parameters
ITT Population

The MEANS Procedure

| CREAM NAME | N Obs | Variable | Label | N | Mean | Median | Std Dev | Minimum | Maximum |
|---|---|---|---|---|---|---|---|---|---|
| Efudex® | 11 | cmax | Cmax (ng/mL) | 11 | 5.8945455 | 3.5800000 | 4.1302575 | 1.6600000 | 13.2000000 |
| | | tmax | Tmax (hr) | 11 | 1.0000000 | 1.0000000 | 0 | 1.0000000 | 1.0000000 |
| TRADENAME | 13 | cmax | Cmax (ng/mL) | 13 | 3.6600000 | 3.4100000 | 1.5778678 | 1.1100000 | 7.3500000 |
| | | tmax | Tmax (hr) | 13 | 1.4615385 | 1.0000000 | 1.3913653 | 1.0000000 | 6.0000000 |

**Table 4: $C_{max}$ and $T_{max}$ for all subjects in the PK populations**

Table 14.2.3
Summary Statistics of Pharmacokinetic Parameters
PK Analysis Population

The MEANS Procedure

| CREAM NAME | N Obs | Variable | Label | N | Mean | Median | Std Dev | Minimum | Maximum |
|---|---|---|---|---|---|---|---|---|---|
| Efudex® | 10 | cmax | Cmax (ng/mL) | 10 | 6.1750000 | 4.1050000 | 4.2418320 | 1.6600000 | 13.2000000 |
| | | tmax | Tmax (hr) | 10 | 1.0000000 | 1.0000000 | 0 | 1.0000000 | 1.0000000 |
| TRADENAME | 13 | cmax | Cmax (ng/mL) | 13 | 3.6600000 | 3.4100000 | 1.5778678 | 1.1100000 | 7.3500000 |
| | | tmax | Tmax (hr) | 13 | 1.4615385 | 1.0000000 | 1.3913653 | 1.0000000 | 6.0000000 |

For subjects who did have quantifiable levels of plasma fluorouracil, the time points at which these levels were detected were between the 1 - 4 hour post-dose time points. No subject had detectable levels of plasma fluorouracil after 10 hours. Approximately equivalent proportions of subjects in each treatment group had quantifiable levels of plasma fluorouracil at 1, 2 and 4 hours post-dose. Summary statistics for $C_{max}$ and $T_{max}$ are displayed by population and treatment group below in Table 5.

**Table 5: Summary Statistics of Pharmacokinetic Parameters**

| | **Treatment Group** | |
|---|---|---|
| | **4% TOLAK** | **Efudex®** |
| **ITT Population** | **N=13** | **N=11** |
| $C_{max}$ (ng/mL) | | |
| Mean (SD) | 3.66 (1.578) | 5.89 (4.130) |
| Range | 1.11 – 7.35 | 1.66 – 13.20 |
| $T_{max}$ (hr) | | |
| Mean (SD) | 1.46 (1.391) | 1.00 (0) |
| Range | 1.0 – 6.0 | 1.00 – 1.00 |
| **PK Population** | **N=13** | **N=10** |
| $C_{max}$ (ng/mL) | | |
| Mean (SD) | 3.66 (1.578) | 6.18 (4.242) |
| Range | 1.11 – 7.35 | 1.66 – 13.20 |
| $T_{max}$ (hr) | | |
| Mean (SD) | 1.46 (1.391) | 1.00 (0) |
| Range | 1.0 – 6.0 | 1.00 – 1.00 |

*N = Maximum number of plasma samples above LLOQ of 1.0 ng/mL*

Systemic exposure of fluorouracil did not exceed the reference product following treatment of subjects with the proposed product once daily for up to 28 days compared to treatment with Efudex® twice daily for up to 28 days. Based on the limited data available, $C_{max}$ after once daily 4% TOLAK application was lower compared to twice daily Efudex® applications, which is expected as almost half of fluorouracil was applied from the proposed product compared to the reference product, Efudex®. Though there is difference between Tmax in two treatment groups, but given the chronic topical use of the products, the difference should not be clinically relevant.

Safety Results: According to the sponsor, all subjects in each treatment group experienced at least one treatment emergent adverse event. Most AEs were considered either mild or moderate in intensity. One (4.8%) subject in the 4% TOLAK treatment group and 3 (13.6%) subjects in the Efudex® treatment group reported AEs that were considered severe in intensity. The most common AEs (reported in more than 2 subjects in a treatment group) include headache, insomnia and skin disorder AEs, including erythema, pruritus, skin burning sensation, pain of skin, scab, skin exfoliation and skin haemorrhage.

No clinically significant changes in vital signs from screening to discharge were noted to have occurred for any subjects during the study.

**Overall Conclusions:**

Pharmacokinetic Conclusions:

- The majority of plasma samples from subjects in both treatment groups did not have detectable levels of fluorouracil which reflects the low level of systemic absorption of topical fluorouracil for both formulations, though, the majority of subjects did have at least 1 positive plasma sample.
- The frequency of plasma samples with undetectable levels of fluorouracil was similar between treatment groups.
- For subjects in the PK population with measurable levels of plasma fluorouracil, the mean (SD) $C_{max}$ was 3.66 (1.578) and 6.18 (4.242) ng/mL for subjects in the 4% TOLAK and Efudex® treatment groups, respectively, and the mean (SD) $T_{max}$ was 1.46 (1.391) and 1.00 (0) hours for subjects in the 4% TOLAK and Efudex® treatment groups, respectively.
- Systemic exposure of fluorouracil did not exceed the reference product following treatment of subjects with the proposed product once daily for up to 28 days compared to treatment with Efudex® twice daily for up to 28 days.

***Reviewer's Comment:*** *The reviewer agrees that based on the limited data available, systemic exposure of fluorouracil did not exceed the reference product following treatment of subjects with the proposed product once daily for up to 28 days compared to treatment with Efudex® twice daily for up to 28 days. The data demonstrates that $C_{max}$ after once daily 4% TOLAK application was lower compared to twice daily Efudex® applications, what was expected as almost half of the fluorouracil was applied from the once daily proposed product compared to twice daily reference product, Efudex®.* Therefore, systemic safety of fluorouracil from TOLAK following once daily application *should not be worse than the already marketed Efudex® product that is applied twice daily.*

## 4.2 Filing Review Form

### Office of Clinical Pharmacology

*New Drug Application Filing and Review Form*

**General Information About the Submission**

| | Information | | Information |
|---|---|---|---|
| **NDA Number** | **22-259** | **Brand Name** | |
| **DCP Division** | **III** | **Generic Name** | **Tradename (5-Fluorouracil) 4% Cream** |
| **Medical Division** | **540** | **Drug Class** | **Antimetabolite** |
| **DCP Reviewer** | **Tapash K. Ghosh** | **Indication(s)** | **Actinic keratosis** |
| **DCP Team Leader** | **Sue-Chih Lee** | **Dosage Form** | **Topical cream** |
| | | **Dosing Regimen** | **qd** |
| **Date of Submission** | **8/20/07** | **Route of Administration** | **Topical** |
| **Estimated Due Date of OCP Review** | **03/20/07** | **Sponsor** | **Hill Dermaceuticals** |
| **PDUFA Due Date** | **6/20/08** | **Priority Classification** | **3S** |
| **Division Due Date** | **5/20/07** | | |

**Clin. Pharm. and Biopharm. Information**

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | **X** | | | |
| **Tabular Listing of All Human Studies** | **X** | | | |
| **HPK Summary** | **X** | | | |
| **Labeling** | **X** | | | |
| **Reference Bioanalytical and Analytical Methods** | **X** | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| **Healthy Volunteers-** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Patients-** | | | | |
| single dose: | | | | |
| multiple dose: | X | 1 | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |

| | | | | |
|---|---|---|---|---|
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | **1** | | |
| | | | | |

**Filability and QBR comments**

| | **"X" if yes** | **Comments** |
|---|---|---|
| **Application filable ?** | **X** | Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one? |
| **Comments sent to firm ?** | | Comments have been sent to firm (or attachment included). FDA letter date if applicable. |
| **QBR questions (key issues to be considered)** | **Does the proposed 5 -FU cream have adequately evaluated systemic exposure?** | |
| **Other comments or information not included above** | | |
| **Primary reviewer Signature and Date** | Tapash Ghosh | |
| **Secondary reviewer Signature and Date** | Sue-Chih Lee | |

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

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/s/
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Tapash Ghosh
4/18/2008 04:34:16 PM
BIOPHARMACEUTICS

Dennis Bashaw
4/18/2008 04:53:27 PM
BIOPHARMACEUTICS