CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
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Division / Office	DDDP/ ODEIII
Reviewer Name(s)	Amy S. Woitach, D.O., M.S.
Review Completion Date	08/14/15
Established Name	Fluorouracil cream, 4%
(Proposed) Trade Name	Tolak Cream, 4%
Therapeutic Class	Nucleoside metabolic inhibitor
Applicant	Hill Dermaceuticals, Inc.
Formulation(s)	Topical cream
Dosing Regimen	Once daily application for four weeks, as tolerated
Indication(s)	Topical treatment of actinic keratosis lesions of the face, ears, and scalp
Intended Population(s)	Adults, eighteen years of age and older

Template Version: March 6, 2009

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Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 8

1.1 Recommendation on Regulatory Action 8
1.2 Risk Benefit Assessment 8
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies 9
1.4 Recommendations for Postmarket Requirements and Commitments 9

2 INTRODUCTION AND REGULATORY BACKGROUND 9

2.1 Product Information 9
2.2 Currently Available Treatments for Proposed Indications 9
2.3 Availability of Proposed Active Ingredient in the United States 10
2.4 Important Safety Issues With Consideration to Related Drugs 10
2.5 Summary of Presubmission Regulatory Activity Related to Submission 10
2.6 Other Relevant Background Information 10

3 ETHICS AND GOOD CLINICAL PRACTICES 10

3.1 Submission Quality and Integrity 10
3.2 Compliance with Good Clinical Practices 11

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 11

4.1 Chemistry Manufacturing and Controls 11
4.2 Clinical Microbiology 12
4.3 Preclinical Pharmacology/Toxicology 12
4.4 Clinical Pharmacology 12
4.4.1 Mechanism of Action 12
4.4.2 Pharmacodynamics 13
4.4.3 Pharmacokinetics 13

5 SOURCES OF CLINICAL DATA 13

5.1 Studies/Clinical Trial(s) 13
5.2 Review Strategy 13
5.3 Discussion of Individual Studies/Clinical Trials 13

6 REVIEW OF EFFICACY 14

Efficacy Summary 14
6.1 Indication 15
6.1.1 Methods 15
6.1.2 Demographics 15
6.1.3 Subject Disposition 15
6.1.4 Analysis of Primary Endpoint(s) 15
6.1.5 Analysis of Secondary Endpoints(s) 17
6.1.6 Other Endpoints 17

6.1.7 Subpopulations....17
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations....17
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects....17
6.1.10 Additional Efficacy Issues/Analyses....17

7 REVIEW OF SAFETY....17

Safety Summary....17
7.1 Methods....18
7.1.1 Studies/Clinical Trials Used to Evaluate Safety....18
7.1.2 Categorization of Adverse Events....19
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence....19
7.2 Adequacy of Safety Assessments....19
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations....19
7.2.2 Explorations for Dose Response....19
7.2.3 Special Animal and/or In Vitro Testing....19
7.2.4 Routine Clinical Testing....20
7.2.5 Metabolic, Clearance, and Interaction Workup....20
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class...20
7.3 Major Safety Results....20
7.3.1 Deaths....20
7.3.2 Nonfatal Serious Adverse Events....20
7.3.3 Dropouts and/or Discontinuations....21
7.3.4 Significant Adverse Events....21
7.3.5 Submission Specific Primary Safety Concerns....22
7.4 Supportive Safety Results....22
7.4.1 Common Adverse Events....22
7.4.2 Laboratory Findings....23
7.4.3 Vital Signs....23
7.4.4 Electrocardiograms (ECGs)....23
7.4.5 Special Safety Studies/Clinical Trials....23
7.4.6 Immunogenicity....23
7.5 Other Safety Explorations....23
7.5.1 Dose Dependency for Adverse Events....23
7.5.2 Time Dependency for Adverse Events....23
7.5.3 Drug-Demographic Interactions....23
7.5.4 Drug-Disease Interactions....24
7.5.5 Drug-Drug Interactions....24
7.6 Additional Safety Evaluations....24
7.6.1 Human Carcinogenicity....24
7.6.2 Human Reproduction and Pregnancy Data....24
7.6.3 Pediatrics and Assessment of Effects on Growth....24
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound....24

7.7 Additional Submissions / Safety Issues 24

8 POSTMARKET EXPERIENCE 25

9 APPENDICES 26

9.1 Literature Review/References 26
9.2 Labeling Recommendations 26
9.3 Advisory Committee Meeting 26

Table of Tables

Table 1: Agency Assessment of Recurrence in Study 50.....17
Table 2: Adverse Event Summary for Long Term Safety Study 50.....22

Table of Figures

No table of figures entries found.

APPEARS THIS WAY ON ORIGINAL

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This NDA was originally submitted on August 17, 2007, with a PDUFA goal date of June 20, 2008. The applicant proposed a new concentration of fluorouracil cream, 4%, and conducted a 505 (b)(2) development program establishing a clinical bridge to Efudex Cream 5%. 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. Two clinical trials demonstrated superiority of the proposed 4% cream to its vehicle, and no review issues were identified except for those related to product quality.

In reviews from June 2008, Dr. Markham C. Luke, Lead Medical Officer and Cross-Discipline Team Leader and Dr. David Kettl, the Primary Clinical Reviewer recommended that this application should be approved from a clinical perspective. Following closure of the primary and CDTL reviews, the Agency CMC team identified issues during facility inspections that led to issues regarding veracity of data and application integrity. However a Compete Response was issued on 6/29/09 due to CMC issues on identity, strength, purity, and quality of the product.

The applicant had an ongoing open-label study at the time of the original submission: HD-FUP4LTS-050 (which will be referred to as study 50): An open-label, multi-center, long-term safety study of 4% Tolak cream in subjects with actinic keratosis who participated in the Phase 3 studies. Data from this trial was submitted as an amendment nearly nine months into the original review cycle (5/7/2008). The datasets for this study were not submitted in a usable format. Due to the lateness of the amendment in the original review cycle, the lack of usable datasets, and the pending Complete Response action, Study 50 was not reviewed in the initial review cycle.

In addition to the CMC data provided with this resubmission, clinical trial data from study 50 was also reviewed in this cycle. The applicant submitted proposed labeling that includes results from this 12-month follow-up study. The focus of this clinical review evaluates the safety and efficacy data from trial 50.

With this resubmission the applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product as per Dr. Jane Chang's 7/30/15 review. Also, no issues were identified in the open-label study to preclude the prior clinical recommendation of approval. As of the date of this review, a recommendation from the Office of Process and Facility on the site acceptability has not been made. Labeling negotiation is currently ongoing as well. The NDA resubmission

appears to be approvable from a clinical perspective, once the above pending issues are resolved. There are no clinical PMRs recommended for this NDA. The applicant is requesting that the Agency allow them to market the first 2 validation batches with the original carton and container labels. They are proposing an overlay to cover the statement "For the treatment of Actinic Keratosis". This approach has been found acceptable by DMEPA and this reviewer. Future revised carton and container labeling address the Agency's recommendations.

1.2 Risk Benefit Assessment

The risk benefit assessment remains the same as in the original clinical review.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No specific post-marketing risk management activity is recommended at this time for Tolak Cream, 4%. Labeling is adequate to convey the risks of this product.

1.4 Recommendations for Postmarket Requirements and Commitments

No specific post-marketing studies are recommended at this time for Tolak Cream, 4%.

2 Introduction and Regulatory Background

This NDA is a 505(b)2 application for a new concentration of fluorouracil in a topical cream. Tolak is a 4% cream product and is compared to Efudex Cream, 5% in this application. This application borrows the FDA's findings of systemic safety for the referenced Efudex product with conduct of clinical and pharmacokinetic comparability studies.

Two phase 3 trials were conducted in support of this NDA. HD-FUP3B-048 was designed to evaluate the efficacy and safety of once daily application over four weeks of Tolak (fluorouracil) Cream 4% compared with four week applications of twice daily applications of Efudex 5% cream, Efudex vehicle, and Tolak (fluorouracil) vehicle. While noninferiority to Efudex was not demonstrated, superiority to vehicle was statistically demonstrated.

HP-FU3S-049 was designed to evaluate the efficacy and safety of once daily application of Tolak (fluorouracil) Cream 4% compared with Tolak (fluorouracil) vehicle. Statistical superiority to vehicle was again demonstrated in this second study. These

two studies were submitted as the basis of efficacy demonstration in this application, and were reviewed in the initial cycle.

In reviews from June 2008, Dr. Markham C. Luke, Lead Medical Officer and Cross-Discipline Team Leader and Dr. David Kettl, the Primary Clinical Reviewer recommended that this application should be approved from a clinical perspective. However a Compete Response was issued on 6/22/09 due to CMC issues on identity, strength, purity, and quality of the product. The initial CMC review was amended in a review addendum dated June 18, 2008, by Dr. Shulin Ding. The recommendation for approval was changed based on:

> "The Overall Compliance Recommendation (attachment) from the Office of regarding facility cGMP status was issued on June 10, 2008, and the recommendation is "Withhold" for this NDA. The overall recommendation of "withhold" indicates the lack of cGMP compliance in the manufacture of the proposed product. Without an acceptable cGMP compliance, the identity, strength, purity, and quality of the product cannot be assured."

A second CMC review was signed into DFS on May 21, 2009. As outlined in the second CMC review, the September 2008 establishment inspection revealed major deficiencies in cGMP compliance as well as deficiencies in the drug product stability data. The establishment inspection took place from September 15, 2008 to September 29, 2008. Out of specification (OOS) results were reported for the two recent lots of bulk drug and one lot of the packaged product. The OOS results suggested that the manufacturing process was not well controlled.

On November 30, 2011, The Agency sent an "Issuance of Consent Decree with Application Integrity Policy provisions". Review of this application did no continue until November, 2014, when the District office determined that due to "unique circumstances", review of this application could resume.

Almost all of the clinical data had been reviewed during the initial cycle, and the pivotal studies will not be revisited in this review. The conclusion of the reviews in the initial cycle was that safety and efficacy for the proposed indication had been adequately demonstrated. The only new clinical information is related to the long term open label study 050, and that will be the subject of this review. The Complete Response action in 2009 contained issues solely related to CMC and product quality, including data integrity.

The applicant had an ongoing open-label study at the time of the original submission. With the response to the CR, the applicant included additional CMC data and new clinical data for the now completed, open-label study. A major amendment was

received on March 23, 2015 extending the PDUFA goal date to September 18, 2015. This clinical review will focus on the data from the open-label study.

2.1 Product Information

Refer to the 6/2/2008 clinical review by Dr. David Kettl.

2.2 Currently Available Treatments for Proposed Indications

Refer to the 6/2/2008 clinical review by Dr. David Kettl. Additional products approved since 2008 include the following:

> PICATO (Ingenol mebutate) Gel 0.015%, Gel 0.05% for the treatment of actinic keratosis

2.3 Availability of Proposed Active Ingredient in the United States

Refer to the 6/2/2008 clinical review by Dr. David Kettl.

2.4 Important Safety Issues with Consideration to Related Drugs

This reviewer concurs with Dr. Kettl's recommendations from the original review that:

> Labeling contraindications will mirror those of the Efudex label, and include pregnancy category of X and use in patients with dihydropyrimidine dehydrogenase (DPH) deficiency.
>
> The vehicle for this application includes (b) (4) peanut oil, and a labeling precaution has been recommended for caution in prescribing Tolak (fluorouracil) Cream to peanut sensitive individuals.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Refer to the 6/2/2008 clinical review by Dr. David Kettl and to introductory paragraph of section 2 above.

2.6 Other Relevant Background Information

The sponsor attempted to modify Section 8 of the label to conform with the Pregnancy Labeling and Lactation Rule (PLLR). However, Tolak cream was submitted prior to the June 30th PLLR effective date; therefore, the PLLR conversion is voluntary at this time. It has been determined that the Tolak cream label will not be revised to conform with the

PLLR at this time. Therefore, Tolak cream labeling will contain the same information as contained in the Efudex cream label, a Pregnancy Category X drug.

3 Ethics and Good Clinical Practices

This section will refer to study 050. For the other clinical studies submitted refer to section 4 in the 6/2/2008 clinical review by Dr. David Kettl.

3.1 Submission Quality and Integrity

The original inspection found application integrity policy (AIP) concerns, including issues with (b) (4). All review activity on this application was stopped due to the AIP. DDDP was informed that review on this application may proceed. A recommendation from the Office of Process and Facility on the site acceptability is pending at the time of this review, so a final recommendation for action for this application cannot be made until closure of the OPQ review.

3.2 Compliance with Good Clinical Practices

The applicant affirmed that the studies were conducted in compliance with the FDA regulations, the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. The investigator and all study staff conducted the study in compliance with this protocol. As noted, final reports regarding facility inspections are pending at the time of this review.

The protocol, informed consent documents, any information provided to subjects, recruitment advertisements and any amendments to these items had IRB approval prior to their use in the study. Voluntary informed consent was given by every subject prior to the initiation of any study-related procedures. The rights, safety and well-being of the study subjects were the most important considerations and prevailed over the interests of science and society.

All personnel involved in the conduct of this study were qualified by education, training and experience to perform their assigned responsibilities.

3.3 Financial Disclosures

It was affirmed that none of the clinical investigators disclosed any proprietary interest in the product, or significant equity interest in the sponsor company. Also, no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to section 3.1 the 6/2/2008 clinical review by Dr. David Kettl for details on the product review from the original submission.

Regarding, the resubmission, Dr. Chang concludes the following:

> This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. However, a recommendation from the Office of Process and Facility on the site acceptability has not been made. Labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is not ready for approval per 21 CFR 314.125(b)(6),(13) in its present form until all issues are satisfactorily resolved.

The original inspection found application integrity policy (AIP) concerns, including issues with (b) (4). Dr. Jessica Cole's 7/22/15 product quality microbiology review recommends approval and finds the following:

- The compendial antimicrobial effectiveness test results are adequate to support approval of this drug product with (b) (4)% methylparabens, (b) (4)% propylparabens, and (b) (4)% BHT.
- The proposed release test specification and test methods are adequate and consistent with industry standards.
- The stability program is adequate, pending receipt of a revised specification (b) (4)

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

No significant Pharmacology/Toxicology review issues have been identified for this NDA resubmission. The sponsor generated a clinical bridge to Efudex (fluorouracil) cream, 5% in the original NDA submission. This clinical bridge allows the Agency to rely on their findings of safety for Efudex cream to support Tolak cream. In addition, the sponsor submitted several nonclinical literature references in the original NDA submission. Adequate nonclinical information has been provided to support Tolak cream.

Dr. Barbara Hill's review concludes that this NDA resubmission appears to be approvable from a Pharmacology/Toxicology perspective; there are no nonclinical PMRs for this NDA.

4.4 Clinical Pharmacology

NDA 22259 was originally submitted on 8/17/2007. The Clinical Pharmacology review was conducted by Dr. Tapash Ghosh and completed on 4/18/2008 with an acceptable recommendation. Dr. Doanh Tran has recommended minor labeling changes in his review of this resubmission.

4.4.1 Mechanism of Action

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

4.4.2 Pharmacodynamics

Not applicable

4.4.3 Pharmacokinetics

Refer to section 5.1 the 6/2/2008 clinical review by Dr. David Kettl.

5 Sources of Clinical Data

This section will refer to open-labelled trial 50; for details on the other clinical studies from the original submission) supporting approval, refer to the 6/2/2008 clinical review by Dr. David Kettl. Dr. Kettl's review includes the randomized control trials 48 and 49 trials which were the lead-in studies for trial 50.

5.1 Studies/Clinical Trial(s)

HD-FUP4LTS-050: An open-label, multi-center, long-term safety study of 4% Tolak cream in subjects with actinic keratosis who participated in the Phase 3 studies.

5.2 Review Strategy

The applicant had an ongoing open-label study at the time of the original submission. Data from this trial was submitted as an amendment nearly nine months into the original

review cycle (5/7/2008). The datasets for this study were not submitted in a usable format. Due to the lateness of the amendment in the original review cycle, the lack of usable datasets, and the pending Complete Response action, Study 50 was not reviewed in the initial review cycle.

This clinical review of the resubmission will focus on long-term safety (with possible reapplication) and efficacy data (assessment of recurrence of AK lesion) from the open-label study.

5.3 Discussion of Individual Studies/Clinical Trials

Study 50 is an open-label, 12-month follow-up study of subjects who were treated with Tolak in either Study 48 or Study 49. Once Studies 48 and 49 were unblinded, subjects who had received Tolak in Study 48/49 (whether or not the subject's lesions were cleared at the end of the study) were enrolled into Study 50.

The first visit in Study 50 was to be at least 6 months after the 4-week post-treatment visit (primary efficacy timepoint / final visit) in Study 48/49. Subjects who had no lesions at the first follow-up visit in Study 50 were to return for an additional follow-up visit scheduled for 12 months after the final visit in Study 48/49. Subjects who had lesions at the first follow-up visit were to be treated at the discretion of the investigator with either Tolak re-treatment or other therapies. Subjects re-treated with Tolak were evaluated at the end of treatment, 4 weeks post-treatment, and 12 months after the final visit in Study 48/49.

The protocol for Study 50 anticipated that 400 subjects would be eligible and willing to participate in the study. (Studies 48 and 49 combined enrolled a total of 403 subjects in the Tolak arm.) The protocol included plans for an interim look at the data once approximately 300 subjects were enrolled in Study 50. The applicant conducted the interim look after 310 subjects had entered Study 50 and 70 subjects completed the Month 12 visit. However, no additional subjects entered the trial after the interim look; the total enrollment of Study 50 was 310 subjects.

Reviewer comment: Dr. Kettl's 2008 clinical review also includes a review of the interim safety data from Study 50.

6 Review of Efficacy

Efficacy Summary

The original application contained two Phase 3 trials (Study 48 and Study 49). Studies 48 and 49 were designed to assess the efficacy and safety of Tolak (fluorouracil) cream 4% in the treatment of actinic keratoses (AK). The original reviews concluded that the

efficacy of Tolak cream 4% had been demonstrated in two studies. Refer to section 6 in the 6/2/2008 clinical review by Dr. David Kettl for details. The conclusion that the efficacy of Tolak in the treatment of AK was demonstrated in two vehicle-controlled studies remains the same.

After the initial look at the data, the applicant created a different definition for assessing recurrence and non-recurrence than was originally planned in the protocol. The review team did not agree with the applicant's definition of recurrence and non-recurrence as the estimates are unreliable and may be biased in favor of increasing the estimate of the non-recurrence rate. Also, because the interval for assessing recurrence for all subjects varied, the Agency's analysis will focus on recurrence at 12 months.

The Agency's analysis found the recurrence rate to be at least 54 % (19% of subjects had no follow up). The AK lesion recurrence rate for Tolak at 12 months appears to be similar to the AK lesion recurrence rate of the approved product Picato (ingenol mebutate).

6.1 Indication

Tolak (fluorouracil) Cream 4% is indicated for actinic keratosis of the scalp, face, and ears if approved.

6.1.1 Methods

The review is based on an evaluation the applicant's clinical study report, Agency analysis of datasets, and proposed labeling.

6.1.2 Demographics

Studies 48 and 49 randomized 403 subjects to the Tolak arm (353 subjects in Study 48 and 50 subjects in Study 49). Of these subjects, 203 were observed to be completely clear of lesions 4 weeks post-treatment and 1 subject was imputed to be completely clear using LOCF, for a total of 204 subjects classified as responders. Of the remaining subjects, 183 were observed post-treatment to have lesions remaining and 16 subjects were imputed using LOCF to have lesions remaining for a total of 199 subjects classified as non-responders.

Approximately 81% of subjects who completely cleared of lesions at the end of Study 48/49 enrolled in Study 50, while approximately 72% of subjects who did not completely clear of lesions at the end of Study 48/49 enrolled in Study 50. Three subjects who did not have and end of study visit in Study 48/49 enrolled into Study 50.

6.1.3 Subject Disposition

310 subjects were enrolled, and 307 completed the study. One subject discontinued following hospitalization and surgery for an ankle fracture after a fall. One moved out of state. The remaining discontinued subject enrolled late and needed to be retreated.

6.1.4 Analysis of Primary Endpoint(s)

The protocol for Study 50 defined recurrence or non-recurrence as follows:

- Subjects with no new AK lesions in the treatment areas upon entry into Study 50 were to be considered to have no recurrence and evaluated again for recurrence 12 months after the completion of Study 48/49.
- Subjects who were completely clear of lesions at the end of Study 48/49, but who had new AK lesions upon entry into Study 50 were considered to have a recurrence.
- Subjects who were not completely clear of lesions at the end of Study 48/49 could be re-treated with Tolak in Study 50. Subjects who were clear of lesions after this additional round of treatment would be assessed for recurrence at the Month 12 visit.

After the initial look at the data, the applicant created a different definition for assessing recurrence and non-recurrence than was originally planned in the protocol. The review team did not agree with the applicant's definition of recurrence and non-recurrence at 6 months as:

The rules for defining recurrence and non-recurrence at Month 12 or overall were even more complex, as they also assessed subjects who received re-treatment with Tolak during Study 50.

Reviewer comment: The biostatistics team finds that the applicant's estimates are unreliable and may be biased in favor of increasing the estimate of the non-recurrence rate. See Dr. Kathleen Fritsch's 8/5/15 review for full details.

Study 50 only enrolled subjects who had received Tolak in Study 48/49, thus enrollment could not begin until Studies 48 and 49 were unblinded. Consequently, those subjects who completed Study 48/49 the earliest generally had to wait more than 6 months before enrollment in Study 50 opened. Some subjects had their '6-month' evaluation as long as 11 months after completing Study 48/49. Nonetheless, the '12-month' evaluation was to be scheduled as close as possible to 12 months after completing Study 48/49, regardless of when the '6-month' evaluation occurred.

Among the subjects who were completely cleared at the end of Study 48/49 and entered Study 50, only 7% (12/166) of subjects had their '6-month' evaluation within a nominal 6 ± 0.5 month window. Most subjects, however, did have their '12-month'evaluation within a nominal 12 ± 0.5 month window

Reviewer comment: Because the interval for assessing recurrence for all subjects varied, the biostatistics team recommends that Agency's analysis focus on recurrence at 12 months. This reviewer finds that this analysis would provide the most clinically useful information.

Dr. Kathy Fritsch, biostatistics reviewer, conducted the analysis and presents the results from Study 50 by summarizing the recurrence outcomes for the full12-month follow-up. To fully capture the best available information regarding the outcomes for all 204 subjects who were 100% clear at the end of Study 48 or 49, Dr. Fritsch recommends classifying subjects as to whether the subjects remained clear, had a recurrence or received alternate treatments, or were lost to follow-up.

Table 1: Agency Assessment of Recurrence in Study 50

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

Source: Biostatistics review, table 3, page6

Reviewer comment: This reviewer concurs with Dr. Fritsch's analysis and finds the data as presented clinically relevant for labeling.

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Study 50 was an open-label follow-up study to estimate recurrence rates. As the study did not include hypothesis testing, subgroup analyses were not conducted.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Study 50 was an open-label follow-up study

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Recurrence of AK lesions at the treatment site is the primary assessment of efficacy in Study 50. Refer to section 6.1.4.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

The applicant conducted an interim look of study 50. As part of the original review cycle, a safety update was submitted on March 19, 2008. A summary report for Study HDFUPLTS- 050, an Open Label, Multi-center, Uncontrolled, Single-group Assignment, Long-term Safety Study of Tolak (fluorouracil) Cream 4% in Subjects with Actinic Keratosis, was presented in the safety update and reviewed by Dr. Kettl's in section 7.2.9 of the 2008 clinical review.

The interim review provided information for the 310 subjects who entered in Study 50 and the 70 subjects who completed the Month 12 visit. No additional subjects entered the trial after the interim look; the total enrollment of Study 50 was 310 subjects.

Subjects were assessed for safety based on adverse event reporting at each evaluation (6 months/ start of trial and 12 months/ end of study). No deaths and few SAEs occurred. Most SAEs were likely due to the pathogenesis that leads to AK, but unlikely related to the treatment. The AEs reported as most likely to be related to treatment were predominantly application site reactions.

The clinical review of the full study report concurs with Dr. Kettl's assessment from the review of the interim study report and finds that:

- The adverse events observed in this long term study were similar to those seen in the two phase 3.
- Most of the adverse events were related to application site reactions, and labeling for existing 5-fluourouracil products reflects this, and draft labeling submitted for this product is similar.
- The discontinuation rate in this population (3%) is less than the 15% rate that discontinued from the phase 3 studies due to adverse events.

- Most of the skin neoplasms seen in long term follow-up were on sites other than scalp, face and ears and are thus unrelated to the topical application of this product.

No additional labeling is recommended based on the safety review of the full study report of study 50.

7.1 Methods

Study 50 is supportive of safety data obtained in pivotal trials. Adverse events were collected at study visit 1 (study entry) and study visit 2 (12 months from end of completion of study 48/49). No other safety assessments were performed.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This review only focuses on the12 month, open-labelled study 50.

7.1.2 Categorization of Adverse Events

All clinical adverse events, whether observed by the investigator or the subject were recorded whether or not they were drug related. Severity was recorded as mild, moderate, or severe. The relationship was assessed by the investigator as either unrelated, unlikely, possible, probable, or related.

In addition to collection of adverse event data, tolerability assessments were conducted that included erythema, scaling/dryness, crusting, pruritus, stinging/burning, edema, and erosions.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable. This review pertains to only one open-labelled study.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall exposure was determined to be adequate for approval in the clinical review of the original NDA submission. With this study, an additional 310 subjects were followed for 12 months. Of the 310 subjects enrolled in the study, 104 subjects re-treated with

study medication during the 12-month safety follow-up period. The mean number of days dosed was 27.8 days and the range was 7-34 days.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

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

Clinical consideration was given to potential toxicity in the in the evaluation of safety in the original clinical review. Refer to Dr. David Kettl's clinical review. Local inflammatory reactions were seen in study 50.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

In Dr. Kettl's original review, postmarketing adverse event (AE) reports for Carac Cream, 0.5% and for the class of topical fluorouracil drug products were analyzed. Clinical consideration was given to potential toxicity in the in the evaluation of safety in the original clinical review. The results from study 50 do not contribute significant additional information.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported

7.3.2 Nonfatal Serious Adverse Events

14 subjects reported 19 serious adverse events, of which 18 were judged by the applicant to be unrelated to study medication. SAEs included:

- Squamous cell carcinoma of the skin (6)
- Basal cell carcinoma (4)
- Keratoacanthoma
- Ankle fracture
- Coronary artery stent insertion
- Aortic aneurysm
- Lentigo maligna
- Angina pectoris
- Gastrointestinal hemorrhage
- Osteoarthritis
- Benign prostatic hyperplasia

The reported non-melanoma skin cancers were assessed to be not related to treatment with the exception of Subject 15-337, judged as "unlikely" to be related:

> A 77 year old male who completed 28 applications of study medications and was noted the next week to have basal cell carcinoma at four different sites (left hand, left ear, right chest, and right forehead). The lesions on his left ear and right chest were already adequately treated (with the study medication), while the lesions on his left hand and right forehead were treated with curettage and electrodessication five months later. No further treatment was required.

Reviewer comment: The other serious adverse events, judged by the applicant as unrelated, included squamous cell carcinomas and basal cell carcinomas. Most of these lesions occurred on body sites distinct from the treated areas and this reviewer concurs with the applicant's assessment. Patients who have AKs are likely to also have SCC and BC due to similar etiologies related to sun exposure.

Subject 19-381, a 76 year-old female experienced a gastrointestinal bleed.

Reviewer comment: Based on the narrative it does not appear to be due to fluorouracil toxicity. She was reported to have melanotic stool due to an ulcer and duodenitis.

7.3.3 Dropouts and/or Discontinuations

310 subjects were enrolled, and 307 completed the study. One subject discontinued following hospitalization and surgery for an ankle fracture after a fall. One moved out of state. The remaining discontinued subject enrolled late and needed to be retreated.

Three subjects discontinued treatment due to local adverse events. Two subjects discontinued the retreatment prematurely due to application site irritation: subject 16-148 after 23 applications, subject 106-83 after 18 applications. One subject 102-394 discontinued the retreatment prematurely due to application site dermatitis after 7 applications.

7.3.4 Significant Adverse Events

There were no significant AEs other than the events described above.

7.3.5 Submission Specific Primary Safety Concerns

Local application site reactions, a class-specific safety concern, were common and mild to moderate in severity. These are described in section 7.4.1 below.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse events, as in the phase 3 studies, were application site erythema, irritation, pruritus, discharge and scabbing. Most (91%) of these local application site reactions were considered mild to moderate in severity.
A summary of adverse events is included in the following table:

Table 2: Adverse Event Summary for Long Term Safety Study 50

	Long-term Safety Study (N = 310)
Subjects with 1 or more events[a], n (%)	57 (18.4)
Number of Events	102
Number of SAEs[b], n (%)	19 (18.6)
Severity[b], n (%)	
Mild	59 (57.8)
Moderate	34 (33.3)
Severe	9 (8.8)
Relationship to Study Medication[b], n (%)	
Unrelated	56 (54.9)
Unlikely	6 (5.9)
Possible	0
Probable	4 (3.9)
Related	36 (35.3)
Most Common AEs[a], n (%)[1]	
General disorders and administration site conditions	23 (7.4)
Application site erythema	9 (2.9)
Application site irritation	7 (2.3)
Application site pruritus	5 (1.6)
Application site discharge	4 (1.3)
Application site scab	4 (1.3)
Neoplasms	13 (4.2)
Squamous cell carcinoma of skin	7 (2.3)
Basal cell carcinoma	4 (1.3)

[a] Proportion based on number of subjects.
[b] Proportion based on number of events.
[1] Counts reflect number of subjects reporting one or more AE classified to MedDRA. At each level of summarization (system organ class or preferred term) subjects are counted only once (under the highest likely attribution)

Source: applicant's table

Reviewer comment: Few AEs and SAEs were reported. The majority were mild and related to application site reactions. No additional labeling based on this study is recommended.

7.4.2 Laboratory Findings

Laboratory assessments were not collected in Study 50 for this topical product.

7.4.3 Vital Signs

Vital sign data was not collected in Study 50 for this topical product.

7.4.4 Electrocardiograms (ECGs)

ECGs were not collected in Study 50 for this topical product.

7.4.5 Special Safety Studies/Clinical Trials

Dermal safety studies were conducted and are described in section 7.1.12 in Dr. David Kettl's clinical review.

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

Study 50, an open-labeled, long term follow-up study did not address any of the safety explorations in this section. Refer to Dr. Kettl's clinical review.

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

Not applicable.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Refer to Section 7.1.11 of Dr. Kettl's clinical review.

7.6.2 Human Reproduction and Pregnancy Data

Refer to Section 7.1.14 of Dr. Kettl's clinical review. No pregnancies were reported in study 50.

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant submitted a full pediatric waiver request based on information that actinic keratoses grow slowly and typically require years to develop in reaction to photodamaged skin.

A full waiver was recommended at the time of the original review. There is no change to the original recommendation as the product is not likely to be used in the pediatric age group. During this cycle, the product was discussed at the Pediatric Review Committee (PeRC) on 07/29/2015 and PeRC agreed with the plan for full waiver in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

Not applicable

8 Postmarket Experience

There is no post-marketing experience to date for this product. There is extensive experience with 5-FU products since the 1960's. Topical formulations with 5-FU are currently approved and marketed.

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

- A revised percentage of recurrence will be proposed based on Agency analysis
- AEs identified in the open-label study appear in proposed labeling from the pivotal studies
- The applicant has addressed all of DMEPA's recommendations in the revised carton and container labeling.
- Refer to Dr. David Kettl's clinical review for other labeling recommendations.

9.3 Advisory Committee Meeting

An advisory committee meeting was not convened for this application.

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/s/

AMY S WOITACH
08/31/2015

DAVID L KETTL
09/01/2015

Summary Review for Regulatory Action

Date	June 16, 2009
From	Susan J. Walker, M.D., F.A.A.D.
Subject	Division Director Review
Number	NDA 22-259
Applicant Name	Hill Dermaceuticals
Date of Submission	August 20, 2007
PDUFA Goal Date	June 20, 2008
Proprietary /USAN Name	Tolak/5-Fluorouracil
Dosage Forms / Strength	Cream/4%
Proposed Indication(s)	Treatment of actinic keratoses
Action	***Complete Response***

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	David Kettl
Statistical Review	Kathleen Fritsch
Pharmacology Toxicology Review	Barbara Hill
CMC Review/OBP Review	Jane Chang
Microbiology Review	N/A
Clinical Pharmacology Review	Tapash Ghosh

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

The applicant has submitted an application for approval of a new concentration of topical fluorouracil (4% cream) for the treatment of actinic keratoses. The clinical development plan conforms to the guidance that was given by the agency for the development of this product, and the product was superior to its vehicle in the treatment of actinic keratoses in two studies.

However, the application did not provide adequate information to assure the identity, strength, purity and quality of the product. Significant deficiencies in the Chemistry, Manufacturing and Controls information provide the primary basis for a Complete Response action, and will be discussed below.

2. Background

The applicant, Hill Dermaceuticals, submitted the original NDA on August 20, 2007. The sponsor provided two apparently adequate and well-controlled studies demonstrating the safety and efficacy of the drug product in the treatment of actinic keratoses, and the results of these two trials formed the basis of the clinical conclusion that the applicant had demonstrated an acceptable risk/benefit profile for the proposed product and indication. At the time of completion of the original clinical and statistical reviews the chemistry review was still open and awaiting the inspection reports. The manufacturing facility was inspected April 22, 2008 to May 01, 2008 and inspectional observations were noted and a form 483 was issued. On June 10, 2008 an overall Office of Compliance recommendation of "Withhold" was issued for this NDA indicating lack of cGMP compliance in the manufacturing of the product. Communications ensued between the Agency and the applicant with the objective of resolving these deficiencies and the facilities were re-inspected in September 2009. Following this inspection the Florida District Office recommended that a Warning Letter should be issued and approval of NDA 22-259 should be denied based upon application integrity issues and the firm's history of non-compliance.

On December 18, 2008 the Office of Compliance issued a second "withhold" recommendation, and on April 29, 2009 a Warning Letter was issued to the applicant citing deficiencies at the drug manufacturing facility in Sanford, Florida and significant deviations from CGMP regulations for Finished Pharmaceuticals.

3. CMC/Device

I have reviewed the original CMC review dated March 31, 2008 and the addendum dated May 21, 2009. I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the drug product and the drug substance. Manufacturing site inspections were not acceptable, and the Office of Compliance has issued a withhold recommendation. Until these issues are fully resolved, it would be reasonable to withhold final conclusions concerning the adequacy of the clinical trial data provided by the applicant to support approval of the new drug application.

The chemistry reviewer has concluded that the information provided in support of this application NDA has not assured the identity, strength, purity and quality of the drug product as required under the regulations. Specific deficiencies include:

Stability data: The stability data submitted are not adequate to establish a specification for the drug product and an expiration dating period. Stability data for the three registration batches showed fluorouracil assays ranging from (b) (4)% to (b) (4)%. The reason for (b) (4) is not provided, however there is a concern regarding (b) (4) of the drug product. The chemistry review details additional specific deficiencies, identified during review of the original application, additional submissions, and during the inspections in 2008. Of note is the chemistry reviewers concern that the sponsor may have provided erroneous information for the HPLC chromatograms used to assess the paraben components of the product, and that the chromatograms may be from an different drug product also manufactured (contract) (b) (4) The reviewer concludes that the entire method validation data for paraben assays are invalid. Concerns regarding this and other possible data integrity issues are being addressed by the Office of Compliance. Should the sponsor resolve the significant issues surrounding the validity of data for the paraben assays, they will be required to provide a stability study with three new primary batches of Tolak Cream.

Hold-Time for Bulk Drug: During the establishment inspection in September 2008 it was determined that "out of specification" results had been reported by the contractor for the homogeneity (fluorouracil) assay for 3 lots. There is no indication that the applicant conducted any root cause investigation with regard to the process, but instead appeared to resubmit samples for additional testing without invalidating the original assay results. The failure of bulk drug to meet in-process controls acceptance criteria raises the question about whether or not the process is adequately controlled.

The hold time of the bulk drug (b) (4) no justification was provided. The issues of bulk drug hold time and whether the in-process samples are representative of the bulk drug (b) (4) should be addressed.

Peanut Oil Issues: The chemistry reviewer concludes that the applicant should provide the following information, and I concur with these recommendations:

- Revise the limit for protein analysis in the peanut oil specification to "for information only".

- Correctly identify the manufacturer of the peanut oil and also the facilities involved in testing.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues.

6. Clinical Microbiology

No clinical microbiology review was done.

7. Clinical/Statistical-Efficacy

Discussion of safety and efficacy will be deferred pending resolution of the cGMP issues. Please see discussion below "11. Other Regulatory Issues". The impact of the ongoing investigations on the integrity of the clinical data provided in support of the application is unknown at this time.

8. Safety

Discussion of safety and efficacy will be deferred pending resolution of the cGMP issues. Please see discussion below "11. Other Regulatory Issues". The impact of the ongoing investigations on the integrity of the clinical data provided in support of the application is unknown at this time.

9. Advisory Committee Meeting

An advisory committee was not convened for this application.

10. Pediatrics

Not applicable

11. Other Relevant Regulatory Issues

Facility Inspections:

The applicant's facility was inspected April 22, 2008 to May 01, 2009 4/22-5/1-08 and 6 Inspectional Observations were provided. An Office of Compliance recommendation of "withhold" was provided on June 10, 2008.

Follow-up inspections were conducted on September 9-29, 2008 and 13 Inspectional Observations were provided at the conclusion of the inspections. On December 01, 2008 the Florida District Office provided a recommendation to CDER Compliance that a Warning Letter be issued to Jerry S. Roth for the manufacture of adulterated prescription drug products and also recommended that the approval of NDA 22-259 be denied based on application integrity issues and significant drug cGMP deviations that were uncovered during the inspection. The Office of Compliance issued a "withhold" on December 18, 2008.

On April 27, 2009 a Warning Letter was issued to Hill Dermaceuticals by the Director, Florida District, stating that CGMP deviations cause Hill prescription drugs to be adulterated under the FDCA. The letter also noted that "FDA is currently evaluating information about your chemistry, manufacturing and controls that you have submitted in new drug applications. You will be informed of our conclusions regarding this CMC information by separate correspondence". Specific information will be included in the Complete Response letter to inform the applicant of the NDA 22-259 CMC deficiencies and the information needed to correct those deficiencies.

DSI Inspections:

A Clinical Inspection summary was received from DSI dated April 14, 2008. Three U.S. sites were routinely inspected, and the DSI report concludes that "overall, the data generated by (these sites) appear acceptable in support of the pending application." At this time there are no specific concerns regarding data integrity issues at the clinical sites. However, the adequacy of the clinical data cannot be fully assessed until the CMC issues have been addressed.

12. Labeling

Labeling discussions have been suspended pending resolution of CMC issues.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action: The applicant will receive a Complete Response action. The issues described above should be adequately resolved prior to product approval.

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/s/

Susan Walker
6/22/2009 01:52:51 PM
DIRECTOR

Medical Officer Review of NDA 22-259
Clinical Review Addendum

NDA: 22-259	**Correspondence Date:** August 17, 2007
Serial Number: 000	**CDER Stamp Date:** August 20, 2007
RPM: Carr	**Clinical Review:** May 29, 2009
	Clinical Team: Kettl/Luke

Sponsor: Hill Dermaceuticals, Inc.
2650 South Mellonville Avenue
Sanford, FL 32773

Drug: Tolak (fluorouracil) Cream 4%

Pharmacologic Category: Nucleoside metabolic inhibitor

Indication: Topical treatment of actinic keratosis lesions of the face, ears, and scalp

Dosage Form and Route of Administration: Topical cream

Regulatory Background:

This document is a clinical review addendum to the original NDA clinical review dated May 1, 2008, and signed by the Division Director in DFS on June 2, 2008, whose comments noted that "Issues pending final resolution include final labeling and finalization of other discipline reviews, including chemistry. An addendum to the medical officer review may be appropriate prior to agency action."

A change in recommendation for the action for this application is warranted following completion of the second CMC review on May 21, 2009. The original clinical review, as well as the CDTL supervisory review by Dr. Luke, contained a recommendation for approval based on the clinical data submitted in the original NDA application. However, both the clinical and CDTL reviews noted that the Office of Compliance recommendations and facility inspection reports were still pending at the time of closure of those reviews. Those findings are now complete, and are fully discussed in the second CMC review by Dr. Jane Chang dated May 21, 2009.

A change in recommendation from Approval to Complete Response is now appropriate for this application based on the failure of one of the manufacturing facilities' compliance with cGMP requirements, and the CMC conclusion that:

> *"This NDA has not assured identity, strength, purity, and quality due to lack of the cGMP compliance, acceptable drug product stability data, and acceptable labeling. The September 2008 establishment inspection revealed major deficiencies on the drug product stability data."*

The applicant, Hill Dermaceuticals submitted the original NDA application on August 17, 2007. Hill submitted a 4% formulation of 5-fluorouracil cream, Tolak (fluorouracil) Cream 4%, for daily topical applications in the treatment of actinic keratoses of the face, scalp and ears. The application was submitted under section 505 (b)(2) and referenced Efudex Cream 5%, currently approved for twice daily dosing in the treatment of actinic keratoses, as the comparator product. 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.

Two phase 3 trials were conducted in support of this NDA. HD-FUP3B-048 was designed to evaluate the efficacy and safety of once daily application over four weeks of Tolak (fluorouracil) Cream 4% compared with four week applications of twice daily applications of Efudex 5% cream, Efudex vehicle, and Tolak (fluorouracil) vehicle. While noninferiority to Efudex was not demonstrated, superiority to vehicle was statistically shown.

HP-FU3S-049 was designed to evaluate the efficacy and safety of once daily application of Tolak (fluorouracil) Cream 4% compared with Tolak (fluorouracil) vehicle. Statistical superiority to vehicle was again demonstrated in this second study. These two studies were submitted as the basis of efficacy demonstration in this application.

The most common adverse events were local application site reactions of irritation, pain, erythema, pruritus and edema. These were not unexpected given the local mechanism of action and previous clinical experience with 5-fluorouracil products. There were no significant non-skin related adverse events demonstrated in the development program.

The results of these two trials formed the basis of the conclusion that the applicant had demonstrated an acceptable risk benefit profile for their proposed product, and the basis for the initial approval recommendation by the clinical review team.

The initial CMC review by Dr. Jane Chang, dated March 31, 2008, recommended approval following resolution of the following issues:

- *An acceptable overall recommendation from the Office of Compliance. Inspection of Hill Dermaceuticals, Inc. facility is still pending.*

- *Submission of acceptable labeling information including immediate container and carton labels and Structured Product Labeling (SPL). To date, SPL has not been submitted.*

The initial CMC review was amended in a review addendum dated June 18, 2008, by Dr. Shulin Ding. The recommendation for approval was changed based on:

"The Overall Compliance Recommendation (attachment) from the Office of Compliance regarding facility cGMP status was issued on June 10, 2008, and the recommendation is "Withhold" for this NDA. The overall recommendation of "withhold" indicates the lack of cGMP compliance in the manufacture of the proposed product. Without an acceptable cGMP compliance, the identity, strength, purity, and quality of the product can not be assured."

Labeling discussions with the applicant were tabled at this stage based on the change in action recommendation and planned to be re-visited in the following review cycle of this application. Inspections of the manufacturing facility was planned and conducted in September, 2008.

A second CMC review was signed into DFS on May 21, 2009. As outlined in the second CMC review, the September 2008 establishment inspection revealed major deficiencies in cGMP compliance as well as deficiencies in the drug product stability data. The establishment inspection took place from September 15, 2008 to September 29, 2008. Out of specification (OOS) results were reported for the two recent lots of bulk drug and one lot of the packaged product. The OOS results suggested that the manufacturing process was not well controlled.

The second CMC review summarizes the inspection findings and approvability issues as follows:

"This NDA has not assured identity, strength, purity, and quality due to lack of the cGMP compliance, acceptable drug product stability data, and acceptable labeling. The September 2008 establishment inspection revealed major deficiencies on the drug product stability data. Therefore, this NDA is recommended not to be approved in its present form per a CMC perspective until the following issues are resolved:

1. One of the facilities involved in the submission is deemed not to comply with cGMP requirements. Satisfactory resolution of any deficiencies of the facility is required to assure identity, strength, purity and quality of the drug product.

2. The stability data submitted to date are not adequate to establish a specification for the drug product and an expiration dating period due to the following deficiencies:

    a. Particle size testing, viscosity, homogeneity, and butylated hydroxytoluene assay are not available for the entire stability studies.
    b. The validity of data for pH can not be assured.
    c. The validity of data for methylparaben and propylparaben assays can not be assured because we have concluded that the chromatograms of the method validation study for (b) (4) provided in the original submission and the February 12, 2008 and April 2, 2008 amendments are not from Tolak Cream

based on the following reasons:

You were informed on January 14, 2008 via FDA Information Request Letter that the method validation data provided in the original submission were not acceptable because Tri-Luma Cream was used in the study. This letter requested you to provide validation data for Tolak Cream. You then submitted the method validation data, which included specificity, accuracy/recovery, and precision/repeatability, in the February 12, 2008 and April 2, 2008 amendments. The method validation protocol was provided only in the April 2, 2008 amendment. The chromatograms provided in each of the amendments (b) (4).

1) During the September 2008 establishment inspection, you confirmed that the clinical lot, K050158, was used for evaluation of method precision/repeatability. However, the six chromatograms of the precision/repeatability study (HPLC Bin # 100-105) do not match the release data of Lot K050158 (HPLC Bin # 40-45), but rather they resemble (b) (4), Lot G080139 (HPLC Bin # 36-37 and 41-44).

For instance, a small but distinctive peak with the retention time of (b) (4) minutes is present in all six chromatograms of the release data for (b) (4) Lot G080139. This peak is also present in all of the Tolak Cream chromatograms for the precision/repeatability study, but it is missing in the release data of Tolak Cream, Lot K050158.

2) During the September 2008 establishment inspection, you stated that the "placebo cream" contained 5-fluorouracil and was prepared using the same formulation as that of Tolak Cream except for the absence of methylparaben and propylparaben. You also stated that the chromatograms labeled with "Blank 1" (HPLC Bin # 99) and "Blank 2" (HPLC Bin # 100) were those of "vehicle cream without parabens".

However, the chromatograms of "vehicle cream without parabens" looked more like (b) (4) than that of Tolak Cream without parabens. For example, a major peak (b) (4) minutes) prior to the methylparaben is present in the release data of Tolak Cream, Lot K050158, but it is missing in "Blank 1" or "Blank 2". Since the "vehicle cream without parabens" contains all ingredients in Tolak Cream but the parabens, the chromatograms are expected to resemble that of Tolak Cream except for the absence of the two paraben peaks (retention times at (b) (4) minutes).

3) During the September 2008 establishment inspection, you confirmed that four lots of fluorouracil cream varying the amounts of parabens at (b) (4)%, respectively, of the target concentrations

in the Tolak formulation, were produced. The differences to make the formula to 100% was added or subtracted (b) (4) in the formula. These four creams were used for evaluation of method accuracy/recovery.

Because the (b) (4) minutes peak is present, the chromatograms of the four creams for the accuracy/recovery study (HPLC Bin # 117-118, 21-22, 58-59, and 63-64) also resemble those of (b) (4), Lot G080139. Furthermore, the HPLC chromatograms of the four creams suggest that they are (b) (4) diluted at four different target concentrations. This is because the area counts of all other peaks (e.g. (b) (4) minutes) increase along with the increase of paraben concentrations. If the four creams had been prepared in the manner you have claimed, the HPLC chromatograms would have shown an increase of only methylparaben and propylparaben area counts at higher paraben concentrations and the area counts of all other peaks would have remained the same.

Therefore, unless you provide a satisfactory explanation for why you repeatedly provided (b) (4) data for the accuracy/recovery and precision/repeatability studies and used (b) (4) data as "placebo cream", the validity of the data for methylparaben and propylparaben assays can not be assured.

In addition, you will also need to address the following items in order to provide assurance of the validity of your submitted data for methylparaben and propylparaben assays:

- Explain why the validation report dated February 8, 2008, that was submitted in the February 12, 2008 amendment differed from the same validation report dated February 8, 2008, that was submitted in the April 2, 2008 amendment. The differences include, but are not limited to, table of contents, authorized signatories' signatures, and the contents for the specificity study.

- Explain why you provided a validation report without all authorized signatories' signatures in the February 12, 2008 amendment. The report was signed off only by Sarah Reinartz, Quality Assurance Manager, on February 8, 2008. In addition, the "Report Approval" on page 1 was listed as "Protocol Approval" in the Table of Contents. Pages 5 and 6 of this validation report were missing.

- Explain why the method specificity study submitted in both amendments was conducted two years prior to the approval of the validation protocol. The validation protocol was signed off on January 17, 2008 by Nancy Puglia, Plant Manager, Sarah Reinartz, Quality Assurance Manager, Kacy McGee, Quality Assurance, and Ingrid Warner, Regulatory CMC.

The method specificity study, which included [redacted] chromatograms of methylparaben and propylparaben standards (HPLC Bin # 92-96) and [redacted] chromatograms of "placebo cream", was conducted on October 25, 2005.

- Explain why deviations from the approved validation protocol were not documented in the validation reports submitted in the February 12, 2008 and April 2, 2008 amendments. The deviations included the date of the specificity study, described above, and missing chromatograms of Tolak Cream for the specificity study as required on page 4 (Actual drug product) of the validation protocol. The validation report submitted in the April 2, 2008 amendment was signed on February 8, 2008, by the same personnel on the validation protocol dated January 17, 2008.

- Explain why laboratory preparations of "vehicle cream without parabens" and the four creams used in the method accuracy/recovery study were not documented.

If the above issues are satisfactorily resolved, then stability data from three new primary batches of Tolak Cream should be provided. The data should cover minimum time periods of 12 months for the long-term and 6 months for the accelerated conditions at the time of resubmission. The stability study should follow the drug product stability protocol provided in the March 4, 2008 amendment.

3. The hold time for the bulk drug product [redacted] should be determined and justified. In-process samples taken at the beginning and end of the hold time should be tested per Tolak Cream In-process Product Specification Form (provided in the February 12, 2008 amendment) to justify the hold time.

4. Regarding the peanut oil, NF specification:

   a. Revise the limit for protein analysis in the peanut oil specification to "for information only". The analytical method, i.e. DSFS D-12 for Protein Analysis Sample Preparation and Amino Acid Analysis Protocol, has not been validated properly.

   b. Change the "Approved Manufacturer" from "[redacted]" to "[redacted]".

   c. Several testing facilities are listed as approved testing facilities on your raw material specification forms. For example, Hill Laboratories, Inc., [redacted] are listed as the approved testing facilities in the peanut oil, NF raw material specification form. Please clarify whether all these facilities are involved in the testing of the peanut oil and in what capacity."

Based on the conclusion that the manufacturing process of the proposed product lacks cGMP compliance, and that drug product stability data was not adequate, and concerns regarding data integrity, the CMC review recommendation changed from the initial review recommendation of "approval", to a "complete response" until the issues listed above are satisfactorily resolved.

This reviewer concurs with the above change in recommendation and now proposes that a Complete Response action be taken on this application. All of the CMC listed issues should be satisfactorily addressed and the applicant should demonstrate evidence of successful inspections prior to resubmission of the application to the Agency.

Should the applicant successfully rectify all the facility issues that are outstanding as noted above from the CMC review, the Division should reserve the opportunity to reanalyze the study data from the clinical trials previously submitted in the original application and determine their appropriateness to demonstrate the safety and effectiveness of their fluorouracil product. Such a determination should be withheld until the applicant responds to the Complete Response now recommended for this application. Product quality concerns will need to be adequately addressed, and data integrity issues are still extant. Therefore, the acceptability of the pivotal trial data is still in question.

The Agency ORA Florida District Office recommended to CDER on January 30, 2009, that the Agency should:

> "…invoke the Application Integrity Policy (AIP) for NDA-22-259, 4% 5-Flurouracil 40 g Cream (Tolak Cream, 5-FU), submitted by Hill Dermaceuticals, Inc., Sanford, FL. The firm operates as a manufacturer and distributor of prescription dermatological drugs. The recommendation to invoke the AIP is based on the firm's submission of what we believe to be fraudulent material data to the Agency, the unreliability of firm personnel responsible for the collection of study data, and the firm's system-wide failure to establish and implement standard operating procedures to ensure the integrity of the submitted data and compliance with drug CGMP regulations as revealed during the current inspection of the firm on 9/15-29/08. Moreover, the firm's response of 10/31/08 to the 483 made no commitment to cease the manufacture and distribution of any of the firm's drug products or to increase the frequency and/or robustness of the firm's API and finished drug product testing operations until such time that the firm's manufacturing and analytical processes, procedures, methods, etc., had been satisfactorily implemented, qualified, and/or validated to ensure the safety and effectiveness of the prescription drugs manufactured and distributed by the firm."

The Florida District Office sent on April 27, 2009 a Warning Letter to Hill advising them of the finding that

> "the inspection revealed significant deviations form the Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21 Code of Federal Regulations Parts 210 and 211.
>
> These CGMP deviations cause your prescription drugs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act) [21 USC 351 (a)(2)(B)], in the methods used in, or the procedures or controls used for, the manufacture, processing, packing, and holding of drug products do not conform with the CGMP regulations."

The Warning Letter also notes that the responses submitted by the applicant in response to the Form 483 issued September 29, 2008 documenting the inspection violations were incomplete.

At this writing, the Division is awaiting a report on the applicant's response to the District Office Warning Letter and a determination for the recommendation regarding data integrity has not yet been made.

Reviewer Recommendation:

There is sufficient documentation in the record to conclude a Complete Response action is warranted for this application. Substantial issues revealed during the facility inspections, the CMC review of stability data as well as data integrity concerns dictate that the application cannot be approved in this review cycle. This recommendation has changed from the initial clinical review from May 1, 2008.

An action letter should be sent to the sponsor detailing that the above issues from the second CMC review need to be completely addressed and that facilities inspections involved in the manufacturing of the drug product should be successfully completed prior to resubmission of this application. Such resubmission should assure the Agency that if the applicant wishes to rely on the clinical trial data previously submitted in this initial review cycle, the drug products utilized in those clinical trials were deemed in compliance with cGMP standards and are found adequate on which to base a finding of safety and effectiveness for their product.

David Kettl, MD
Clinical Team Leader

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/s/

David Kettl
6/8/2009 02:48:09 PM
MEDICAL OFFICER
Clinical Review Addendum

CENTER FOR DRUG EVALUATION AND RESEARCH
MEDICAL NECESSITY DETERMINATION

INSTRUCTIONS

Please evaluate the medical need for this product by answering the questions below. Keep in mind that a medically necessary drug product is a product that is used to treat or prevent a serious disease or medical condition for which there is no other alternative drug that is judged by medical staff to be an adequate substitute. Patient "inconvenience" alone is an insufficient basis to classify a product as medical necessity.

NAME AND HFD NUMBER OF DIVISION -
Name of person(s) making determination_____David Kettl, MD_____
Date of Medical Necessity Request – April 28, 2009

PRODUCT(S): Tolak (fluorouracil) Cream 4% (not approved in the United States; NDA 22-259 submitted August 20, 2007; action pending)

MANUFACTURING FIRM: Hill Dermaceuticals, Inc.
2650 S. Mellonville Avenue
Sanford, FL 32773-9311

BACKGROUND:

The Office of Compliance is considering taking action agains (b) (4)

The Office of Compliance had also requested a medical necessity determination for NDA 22-259, Tolak (4% 5-FU cream), since it may also be impacted by this AIP issue. Since this is not an approved product, we would be interested in an update on the review status along with your quick assessment of need for this particular product.

1. Is the product used to treat a serious disease or medical condition?

[X] No
[ ] Yes – Explain

Actinic keratoses are lesions that begin in the epidermis in the sun-exposed areas of the body. The lesions appear as rough, scaly patches that range in color form normal skin tone to reddish brown. They are often circumscribed and are usually 1 mm to 2.5 cm in diameter. Patients may present with a single, well defined lesion, or multiple less defined lesions covering a large area of skin.

Lesions are most likely to develop in fair skinned persons living in sunny climates, and disease prevalence increases with age. It has been estimated that 75% of persons 80 years of age and older have actinic keratoses.

The lesions take years to develop and are more common in men than women. Persons with an extensive history of sun exposure are at greatest risk. More than 80 percent of actinic keratoses occur on areas of the skin with the most sun exposure such as the head, neck, forearms, and hands. Most lesions are asymptomatic, but some cause pruritus or burning.

Actinic keratoses are the most common pre-malignant lesions seen by dermatologists, and may be treated for cosmetic reasons, or for relief of associated symptoms, but the most compelling reason for treatment is to prevent the development of squamous cell carcinomas. Most actinic keratoses, however, do not progress to carcinomas.

2. What are the labeled indications for this product?

This product has not been approved as of this date. The submitted indication is for "topical treatment of actinic keratosis lesions of the face, ears, and scalp.

3. Are there important "off label" uses such as those for a serious medical condition?
No

4. Are there generic forms of this product?
[X] No

This product has not yet been approved.

5. Are there alternative products available?
[ ] No
[X] Yes – Please explain the risk(s) and benefit(s) of this alternative product

5-Fluorouracil is available in concentrations ranging from 0.5% to 5%, in topical solutions and creams. Efudex cream, the innovator product, was first approved on July 29, 1970 under NDA 16-831.

A history of marketed topical formulations includes:

Drug:	NDA #:	Initial Approval Date:
Carac Cream 0.5%	20-985	10/27/00
Fluoroplex Solution 1%	16-765	7/31/70 (now discontinued)
Fluoroplex Cream 1%	16-988	8/6/71
Efudex solution 2%	16-831	7/29/70
5-fluorouracil solution 2%	76-526	11/5/03
Efudex Cream, Solution 5%	16-831	7/29/70
Fluorouracil Solution 5%	76-526	11/5/03

The pending application for this 4% formulation failed to show non-inferiority to the reference product, Efudex Cream 5%, and purports to show that Tolak Cream 4% may have a better adverse event profile.

There are, however, multiple alternative therapies available for the treatment of actinic keratoses. Treatment options include ablative (destructive) therapies or topical therapies.

Cryosurgery using liquid nitrogen is the most common modality of treating actinic keratoses, although compressed nitrous oxide or carbon dioxide is also used. Liquid nitrogen is sprayed directly on the lesions or applied using a cotton-tipped applicator. Treatment success correlates with time of application.

Curettage involves mechanically scraping away abnormal tissue using a sharp curette, and requires local anesthesia. Electrosurgery is sometimes used in combination to destroy remaining tissue and to provide hemostasis.

Photodynamic therapy (PDT) involves applying a photosensitizing agent to each actinic lesion, followed by exposure to light of a specific wavelength. This leads to cell death of the treated tissue. Topical aminolevulinic acid, (Levulan Kerastick, DUSA Pharmaceuticals, Wilmington, MA) – PDT was approved by the FDA in December 1999 for actinic keratoses. A second photosensitizer, methyl- aminolevulinic acid (Metvixia, Galderma USA, Ft. Worth Texas), is FDA-approved for treatment of AKs in conjunction with a proprietary broadband red light when used in conjunction with lesion preparation (debridement), but it is not currently marketed.

Topical therapies include several alternatives beyond fluorouracil products. Imiquimod cream 5%, (Aldara) diclofenac gel 3%, (Solaraze) are approved for actinic keratoses. Topical tretinoin (Retin A, and others), salicylic acid, and alpha hydroxy acids are used for treatment, or as part of adjunctive treatment, but are not currently approved for this indication.

Dermabrasion, chemical peels, and laser therapy are also used by a limited number of providers, but none are approved for the actinic keratosis indication.

6. From the above assessment, is this product Medically Necessary? (Please note that this question refers only to the overall Medical Necessity of the product(s), not whether the specific (manufacturer's) product in question is appropriate for continued administration to patients. If the product is determined to be Medically Necessary, an assessment will then be made as to whether the product in question may be used (for instance with additional testing if necessary) to alleviate shortage situations. If it is not appropriate to administer such material to patients then alternative approaches will be examined. When necessary, a separate Health Hazard Evaluation [HHE] will be requested to address newly identified defects, impurities and/or risks associated with this drug.)

[X] No

[ ] Yes (Please state if this is only for specific indications)

Despite the potential for progression to skin carcinomas, the indication is not considered to be life threatening, and multiple modalities for therapy are currently available.

7. Additional comments:

The Office of Compliance issued a recommendation of "withhold" on June 10, 2008, and December 18, 2008.

The CMC review is still in draft at this writing, but is likely to recommend a Complete Response due to the conclusion that "…this NDA has not assured identity, strength, purity, and quality due to lack of the cGMP compliance, acceptable drug product stability data, and acceptable labeling. The September 2008 establishment inspection revealed major deficiencies on the drug product stability data."

DDDP action is pending closure of the CMC review.

8. Signature of person performing this medical necessity determination.

{See appended electronic signature page}

David Kettl, MD — April 28, 2009

Medical Officer, Clinical Team Leader — Date

{See appended electronic signature page}

Susan Walker, MD

Division Director — Date

(MNForm-Revised 10/02)

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/s/

David Kettl
5/8/2009 09:37:55 AM
MEDICAL OFFICER

Susan Walker
5/13/2009 07:46:30 AM
DIRECTOR

Cross-Discipline Team Leader Review
Tolak (fluorouracil) Cream, 4%
NDA 22-259

Date	April 18, 2008, Completed April 28, 2008
From	Markham C. Luke, M.D., Ph.D., Lead Medical Officer, Dermatology
Subject	Cross-Discipline Team Leader Review
NDA #	22-259
Applicant	Hill Dermaceuticals
Date of Submission	August 20, 2007
PDUFA Goal Date	June 20, 2008
Proprietary Name / Established (USAN) names	Tolak (fluorouracil)
Dosage forms / Strength	Cream/ 4%
Proposed Indication(s)	Topical treatment of actinic keratosis lesions of the face, ears, and scalp.
Recommended:	Approval

1. Introduction

This NDA application is a 505(b)2 application for a new concentration of fluorouracil in a topical cream. Tolak is a 4% cream product and is compared to Efudex Cream, 5% in this application. This application borrows the FDA's findings of systemic safety for the referenced Efudex product with conduct of clinical and pharmacokinetic comparability studies.

As the Lead Medical Officer and Cross-Discipline Team Leader for this application, I concur with the findings of Dr. David Kettl the Primary Clinical Reviewer that this application should be approved.

2. Background

Fluorouracil or 5-fluorouracil is an anti-metabolite used as part of various chemotherapy regimens to treat various tumors. The topical formulation has been available for many years in both 5%, 2%, 1% and 0.5% concentrations for the treatment of actinic keratoses. Actinic

keratosis lies in lower end of spectrum of disease for cutaneous squamous cell carcinoma. While there is some controversy regarding its classification as a pre-cancer, it is clear that histological evaluation supports the assessment of actinic keratosis as a keratinocytic dysplasia, at worst, an in situ dysplastic process.

Standard treatments for actinic keratosis include liquid nitrogen cryotherapy, treatment with topical fluorouracil, treatment with topical imiquimod, and treatment with topical sodium diclofenac. Currently approved fluorouracil products include Efudex - NDA 16-831 (5% Cream, 5% Topical Solution, and 2% Topical Solution), Fluoroplex (1% Cream – NDA 16-765, 1% Topical Solution – NDA 16-988), Carac (0.5% Cream – NDA 20-985), and a generic 5% Cream (ANDA 77-524).

3. CMC

The new Cream formulation of fluorouracil is achieved by (b) (4). This product is a mixture that incorporates many excipients, several with issues of allergenicity and contact hypersensitivity. The formulation is (b) (4) butylated hydroxytoluene NF, cetyl alcohol NF, glycerin USP, isopropyl myristate NF, methyl gluceth-10, methylparaben NF, propylparaben NF, (b) (4) peanut oil NF, stearyl alcohol NF, and stearic acid NF (b) (4) sodium hydroxide NF (b) (4) Arlacel-165 (b) (4)

The product is packaged into a 40 g commercial package size. This size should be adequate to allow for daily application to affected areas for 4 weeks.

The Chemistry reviewer, Dr. Jane Chang, indicates that the provided stability data (12 months real-time and 6 months accelerated) is only sufficient to allow a 15 month shelf life for the drug product. This correlates with ICH Q1E. Further storage temperature should be limited to 25 degrees C due to lack of (b) (4) study data.

The CMC review highlights the following as approvability issues:

1) An acceptable overall recommendation from the Office of Compliance. Inspection of Hill Dermaceuticals, Inc. facility is still pending.
2) Submission of acceptable labeling information including immediate container and carton labels and Structured Product Labeling (SPL). To date, SPL has not been submitted.

Facilities review/inspection

Facilities inspection report from the Office of Compliance remains pending as this review is being written. At submission of this NDA, Hill Dermaceuticals had stated that facilities were not ready for inspection. However, when Hill was informed that this was a filing issue, Hill reversed their statement to the effect that the facilities were ready for inspection. Thus, this inspection report is important and necessary prior to any action.

4. Nonclinical Pharmacology/Toxicology

There are no Pharmacology/Toxicology issues that were of concern other than revision of labeling to conform with current standards. No post-marketing study was recommended, e.g. no carcinogenicity study was needed as treatment of actinic keratosis is not usually a chronic indication. Individual lesions of actinic keratosis are treated with eradication of the lesion as a goal. Long-term exposure could inadvertently result from repeated exposure to fluorouracil, however labeling will need to reflect that long-term exposure should be avoided.

This antimetabolite containing product is Pregnancy Category X. Use in women of child-bearing potential is not appropriate and is contraindicated. Alternative therapies such as liquid nitrogen cryotherapy exist to treat actinic keratosis without unnecessary exposure to teratogens.

5. Clinical Pharmacology/Biopharmaceutics

The PK study HDD-FU1206SA compared the steady state plasma concentration profile of fluorouracil in Tolak Cream, 4% vs. Efudex Cream, 5%. Systemic absorption of fluorouracil for Tolak was determined to not exceed that of Efudex in treatment of subjects with the product once daily for 28 days as compared to Efudex twice daily for up to 28 days.

Tolak should not be used twice daily based on lack of information on PK exposure from this drug when used twice daily. Of note Cmax from Tolak used once daily was more than half that of Efudex used once daily (3.66 vs. 5.89 ng/mL respectively). In addition, Tolak had a longer Tmax: 1.46 hours vs. 1 hour with Efudex.

QT prolongation studies were not conducted with Tolak Cream as the Agency's findings of systemic safety are borrowed from that of Efudex Cream. Topical application of fluorouracil results in ng/mL levels of drug substance and may not result in sufficient exposure to be of concern to this regard.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Tolak (fluorouracil) Cream, 4% was found to be superior to its vehicle in the treatment of actinic keratoses in two studies. Tolak Cream, 4% was applied once daily for four (4) weeks by subjects with at least 5 actinic keratoses on the face, scalp, or ears. The primary efficacy endpoint per prior agreement with Hill Dermaceuticals was 100% clearance of lesions at 4 weeks post-treatment. Of note, immediately post-treatment with a topical fluorouracil product is not the optimal time to make any determination about treatment effect due to the presence of profound erythema, scaling, etc.

The results of primary endpoint analysis as evaluated by the Biostatistics reviewer, Dr. Kathy Fritsch is as follows:

Table 1 – 100% Clearance Rates (Studies 048 and 049 – ITT)

	4% 5-FU	Efudex	Vehicle QD	Vehicle BID
Study 048	N=353	N=349	N=70	N=69
100% Clearance	192 (54%)	202 (58%)	3 (4%)	3 (4%)
p-value / LCB		-11.1%[a] -12.8%[b]	<0.001[c]	
Study 049	N=50	--	N=50	--
100% Clearance	12 (24%)		2 (4%)	
p-value			0.004[c]	

[a] 97.5% ITT lower confidence bound for the difference between 4% 5-FU and Efudex
[b] 97.5% PP lower confidence bound for the difference between 4% 5-FU and Efudex
[c] p-value for 4% 5-FU vs. vehicle QD

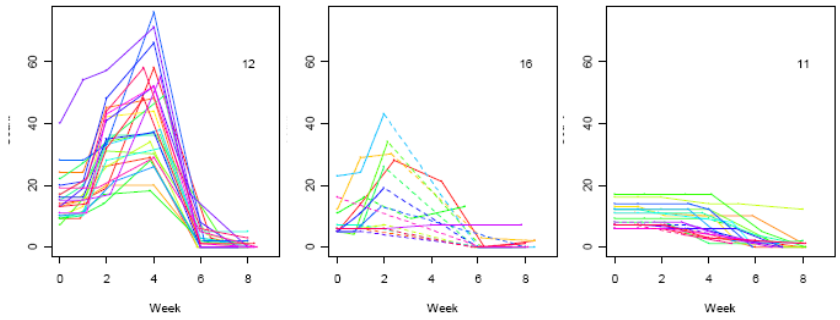
Tolak was also superior to its vehicle for the secondary endpoints of the proportion of patients with at least 75% clearance and the percent reduction of lesions at 4 weeks post-treatment. This was true in both studies.

Both the primary clinical and biostatistical reviewers were in agreement that sufficient efficacy was demonstrated from the clinical studies to allow approval of the product.

While Hill Dermaceuticals has an ongoing 1-year recurrence study, data and a completed study report for this study have not been submitted to the Agency. The clinical reviewer has requested that this be submitted post-approval so as to inform for labeling. Such studies have not been required previously for actinic keratosis products, but Divisional discussion suggest that this is a sufficiently important component of actinic keratosis therapy that such studies should be included for clinical development of these products.

Additional analyses on the impact of dropouts and cross study comparisons of clearance rates are provided in detail in Dr. Fritsch's review. One interesting side analysis is noting that lesion counts rise during treatment as lesions are highlighted by inflammation during treatment. Assessment of lesions can vary from investigator to investigator, which was noted in Figure 5 from Dr. Fritsch's review. However a peak is noted at visit 4, which coincides with peak irritation – see Safety below. These analyses are interesting and have implications for evaluation of topical treatments for actinic keratosis.

Figure 5 - Lesion Count Profiles for 4% 5-FU Subjects for Selected Investigators (Study 048)



Unfortunately, data that is lacking from this submission is the recurrence of lesions after what may be evaluated as effective treatment with Tolak. A longer term (1-year) study of recurrence is pending. The complete study report is requested from the sponsor. This may be reviewed and information added to the labeling post-approval as this was not communicated as a requirement to the sponsor prior to submission. Consideration should be given to the need for recurrence data with this type of treatment for actinic keratosis for future applications.

Of note, the Division of Scientific Investigations has inspected the clinical trial sites and has no recommendations that adversely affect the utility of the clinical data.

8. Safety

The safety database provides valuable data regarding the onset of adverse events in these patients. Of note, these events crescendo at visit number 4 or week number 4 in both studies 48 and 49. Dr. Fritch has provided descriptive graphs that show this nicely:

Figure 9 – Mean Local Tolerance Scores by Visit (Observed Data – Study 048)

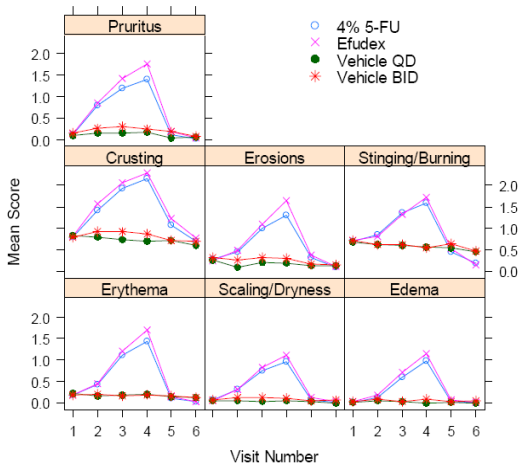
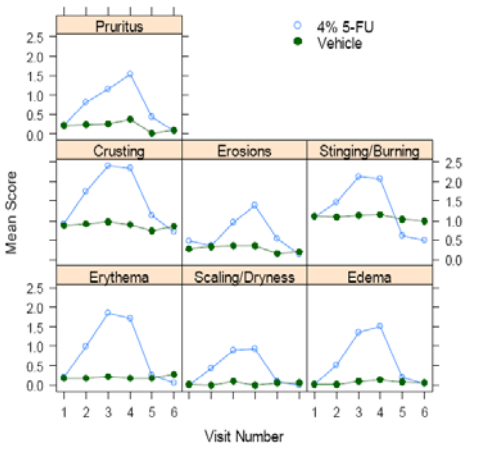


Figure 10 - Mean Local Tolerance Scores by Visit (Observed Data – Study 049)



Most of the adverse events noted are local (see clinical review from Dr. David Kettl). These will be labeled with description by severity. The following table is recommended for inclusion in the Adverse Reactions section of the label:

Table 1 Number and Percentage of Subjects with Monitored Adverse Reactions

	Tolak Adverse Events N=397 n (%)		**Vehicle Adverse Events N=120 n (%)**	
	Mild, Moderate or Severe	**Severe Only**	**Mild, Moderate or Severe**	**Severe Only**
Erythema	394 (99%)	174 (44%)	102 (85%)	0 (0%)
Scaling/Dryness	377 (95%)	94 (24%)	99 (83%)	0 (0%)
Crusting	346 (87%)	87 (22%)	46 (38%)	0 (0%)
Pruritus	337 (85%)	65 (16%)	46 (38%)	1 (1%)
Stinging/Burning	346 (87%)	101 (25%)	42 (35%)	0 (0%)
Edema	275 (69%)	30 (8%)	11 (9%)	0 (0%)
Erosions	271 (68%)	44 (11%)	14 (12%)	0 (0%)

9. Advisory Committee Meeting

No Advisory Committee meeting was held for this original NDA submission.

10. Pediatrics

Actinic keratosis occurs rarely in the pediatric population. The sponsor has requested a waiver from PREA. It is recommended by the clinical review team that this waiver be granted.

Actinic keratosis has been recommended to be added to the list of indications for waiver from PERC.

11. Labeling

The label for Tolak will be the first PLR label for the topical fluorouracil products. As such participation of the SEALD review team was provided and a review of the Patient

Package Insert is underway by the review team in the Office of Surveillance and Epidemiology who performs this review.

The originally proposed proprietary name of [redacted] (b) (4) was found to be unacceptable by the DDMAC reviewers. [redacted] (b) (4) Instead the second proposed name of Tolak was found to be acceptable.

No comparative claims to Efudex were allowed. The single comparative clinical study to Efudex for 505(b)2 bridging purposes was not sufficient to allow comparative claims.

Carton and immediate container labels were submitted late by the sponsor and are currently in the process of being reviewed.

No Medication Guide was required for Tolak Cream due to the lack of serious adverse events that could be mitigated by having a Medication Guide at this time. While severe irritation can result from use of this product, such irritation is not sufficient to be termed serious (i.e. resulting in hospitalization or death).

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The clinical team leader concurs with the primary clinical reviewer that this product may be approved for the treatment of actinic keratosis of the face, ears, and scalp.

- Risk Benefit Assessment

In summary, the benefit-risk of this drug suggests that Tolak Cream, 4% will provide an additional formulation of fluorouracil to be used for treatment of actinic keratosis. However, this product does not provide any additional benefit over already existing products with fluorouracil for topical treatment of actinic keratosis. In fact, the target population for this product could be reduced further by concerns regarding the presence of peanut oil [redacted] (b) (4)

- Recommendation for Postmarketing Risk Management Activities

No specific post-marketing risk management activity is recommended at this time for Tolak Cream, 4%.

- Recommendation for other Postmarketing Study Commitments

No post-marketing commitment is recommended for this action. Treatment of actinic keratosis with topical fluorouracil is not a novel therapeutic approach and the safety profile of such treatment is well understood.

The primary reviewer's mention of the need for a final study report for the sponsor's Study HD-FUPLTS-050 with recurrence rate evaluation of subjects previously treated with Tolak is to be requested.

- Recommended Comments to Applicant

The sponsor is requested to submit Study HD-FUPLTS-050 to the Agency upon completion of their final study report. In addition, changes to the relevant portion of the Clinical Studies section will be needed.

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/s/

Markham Luke
5/6/2008 11:40:05 AM
MEDICAL OFFICER
CDTL review for Tolak (fluorouracil) Cream, 4%. Labeling discussion pending with sponsor. PPI under review.

Susan Walker
6/2/2008 05:17:55 PM
DIRECTOR
Issues pending resolution include labeling and chemistry final review.

CLINICAL REVIEW

Application Type: NDA
Submission Number: 22-259
Submission Code: 000

Letter Date: August 17, 2007
Stamp Date: August 20, 2007
PDUFA Goal Date: June 20, 2008

Reviewer Name: David Kettl, MD
Through:

Review Completion Date: April 15, 2008

Established Name: fluorouracil
(Proposed) Trade Name: Tolak Cream, 4%
Therapeutic Class: Nucleoside metabolic inhibitor
Applicant: Hill Dermaceuticals, Inc.

Priority Designation: S

Formulation: Topical Cream
Dosing Regimen: Once daily application for four weeks, as tolerated
Indication: Topical treatment of actinic keratosis lesions of the face, ears and scalp
Intended Population: Adults, eighteen years of age and older

Table of Contents

1. EXECUTIVE SUMMARY 4
1.1 Recommendation on Regulatory Action 4
1.2 Recommendation on Postmarketing Actions 4
1.2.1 Risk Management Activity 4
1.2.2 Required Phase 4 Commitments 5
1.2.3 Other Phase 4 Requests 5
1.3 Summary of Clinical Findings 5
1.3.1 Brief Overview of Clinical Program 5
1.3.2 Efficacy 6
1.3.3 Safety 6
1.3.4 Dosing Regimen and Administration 7
1.3.5 Drug-Drug Interactions 7
1.3.6 Special Populations 8
2. INTRODUCTION AND BACKGROUND 8
2.1 Product Information 9
2.2 Currently Available Treatment for Indications 9
2.3 Availability of Proposed Active Ingredient in the United States 10
2.4 Important Issues With Pharmacologically Related Products 11
2.5 Presubmission Regulatory Activity 11
3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 12
3.1 CMC (and Product Microbiology, if Applicable) 12
5.5 Hypersensitivity, including Use in Peanut-Sensitive Individuals 14
3.2 Animal Pharmacology/Toxicology 14
4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY 15
4.1 Sources of Clinical Data 15
4.2 Tables of Clinical Studies 16
4.3 Review Strategy 17
4.4 Data Quality and Integrity 18
4.5 Compliance with Good Clinical Practices 18
4.6 Financial Disclosures 19
5. CLINICAL PHARMACOLOGY 19
5.1 Pharmacokinetics 19
6. INTEGRATED REVIEW OF EFFICACY 20
6.1 Indication 20
6.1.2 General Discussion of Endpoints 20
6.1.3 Study Design 21
6.1.4 Efficacy Findings 26
6.1.5 Clinical Microbiology 30
6.1.6 Efficacy Conclusions 30
7. INTEGRATED REVIEW OF SAFETY 31
7.1 Methods and Findings 31
7.1.1 Deaths 32
7.1.2 Other Serious Adverse Events 33
7.1.3 Dropouts and Other Significant Adverse Events 36

7.1.5 Common Adverse Events....42
7.1.6 Less Common Adverse Events....50
7.1.7 Laboratory Findings....51
7.1.8 Vital Signs....53
7.1.9 Electrocardiograms (ECGs)....53
7.1.11 Human Carcinogenicity....53
7.1.12 Special Safety Studies....54
7.1.13 Withdrawal Phenomena and/or Abuse Potential....55
7.1.14 Human Reproduction and Pregnancy Data....56
7.1.16 Overdose Experience....57
7.1.17 Postmarketing Experience....57
7.2 Adequacy of Patient Exposure and Safety Assessments....58
7.2.3 Adequacy of Overall Clinical Experience....58
7.2.8 Assessment of Quality and Completeness of Data....59
7.2.9 Additional Submissions, Including Safety Update....59
7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions....64
7.4 General Methodology....64
7.4.3 Causality Determination....64
8. ADDITIONAL CLINICAL ISSUES....64
8.1 Dosing Regimen and Administration....65
8.2 Drug-Drug Interactions....65
8.3 Special Populations....65
8.4 Pediatrics....65
8.4 Pediatric Use....66
8.7 Postmarketing Risk Management Plan....66
8.8 Other Relevant Materials....67
9. OVERALL ASSESSMENT....69
9.1 Conclusions....69
9.2 Recommendation on Regulatory Action....69
9.3 Recommendation on Postmarketing Actions....70
9.3.1 Risk Management Activity....70
9.3.2 Required Phase 4 Commitments....70
9.3.3 Other Phase 4 Requests....70
9.4 Labeling Review....70
9.5 Comments to Applicant....71
10. APPENDICES....72

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that Tolak (fluorouracil) Cream 4% be approved for the topical treatment of actinic keratosis of the face, ears, and scalp. The applicant has presented adequate evidence from two well controlled studies in subjects with actinic keratoses that this topical product is superior to vehicle when evaluated after four weeks of treatment.

The applicant has submitted under section 505 (b)(2) and has referenced Efudex Cream 5%, currently approved for twice daily dosing in the treatment of actinic keratoses, as the comparator reference product. 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.

The initial phase 3 study failed to show non-inferiority to the referenced product, Efudex Cream 5%, though superiority over vehicle was demonstrated. A second phase 3 study comparing Tolak (fluorouracil) Cream 4% to vehicle was conducted and again confirmed superiority of the drug product to the vehicle.

Due to the clinical bridge established to Efudex Cream 5% via the initial phase 3 study, the applicant has relied on the Agency's findings of systemic safety for the referenced Efudex product. Adequate pharmacokinetic information demonstrating comparable exposure was submitted to complete the systemic safety bridge to Efudex.

The most common adverse events were local application site reactions of irritation, pain, erythema, pruritus and edema. These were not unexpected given the local mechanism of action and previous clinical experience with 5-fluorouracil products.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Risk management will be addressed through labeling. No new safety concerns were

evident in the phase 3 studies performed with topical 5-FU 4% concentration as compared to previously approved formulations containing 5-fluorouracil.

1.2.2 Required Phase 4 Commitments

No recommended clinical phase 4 commitments.

1.2.3 Other Phase 4 Requests

The sponsor should submit the final study report for the long term safety study 050 by six months from the date of action for this application.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Two phase 3 trials were conducted in support of this NDA. HD-FUP3B-048 was designed to evaluate the efficacy and safety of once daily application over four weeks of Tolak (fluorouracil) Cream 4% compared with four week applications of twice daily applications of Efudex 5% cream, Efudex vehicle, and Tolak (fluorouracil) vehicle. While non-inferiority to Efudex was not demonstrated, superiority to vehicle was statistically shown.

HP-FU3S-049 was designed to evaluate the efficacy and safety of once daily application of Tolak (fluorouracil) Cream 4% compared with Tolak (fluorouracil) vehicle. Statistical superiority to vehicle was again demonstrated in this second study. These two studies form the basis of efficacy demonstration in this application.

1.3.2 Efficacy

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.

Study 048 was conducted to demonstrate non-inferiority of Tolak (fluorouracil) Cream 4% to the Efudex Cream 5% and superiority to the Tolak (fluorouracil) vehicle. The study enrolled 841 subjects (353 to Tolak (fluorouracil) Cream 4% once daily, 349 to Efudex 5% twice daily, 70 to vehicle once daily, and 69 to vehicle twice daily) at 26 U.S. centers.

Tolak (fluorouracil) Cream 4% was successful in 54% of subjects compared with 4% of Tolak (fluorouracil) Vehicle subjects ($p<0.001$).

Study 049 was designed to evaluate the efficacy and safety of once daily application of Tolak (fluorouracil) Cream 4% compared with Tolak (fluorouracil) vehicle. No active comparator arm was included in this second phase 3 study. 100 subjects were enrolled across 5 US study sites. Tolak (fluorouracil) Cream 4% was successful in 24% of subjects compared with Tolak (fluorouracil) Vehicle subjects ($p=0.004$).

The treatment effect for the clearance rate was much higher in Study 048 than 049 (Study 048: 54% vs. 4%; Study 049: 24% vs. 4%). The reason for this difference is not clear, though it does not appear to be explained solely by differences in precision afforded by the respective sample sizes (Study 048 enrolled 353 Tolak (fluorouracil) Cream subjects while Study 049 enrolled 50 Tolak (fluorouracil) Cream subjects), or by differences in baseline lesion count (mean of 19.2 for Study 049 vs. 14.4 for Study 048 for 4% 5-FU subjects).

1.3.3 Safety

A total of 829 subjects were exposed to Tolak (fluorouracil) Cream 4% during seven clinical studies from which adverse event and other safety data was collected: three phase 1 safety studies in healthy subjects, two phase 2 trials to assess dose ranging and pharmacokinetic parameters, and two phase 3 trials to evaluate safety and efficacy.

The vast majority of adverse events reported were application site reactions. Most 5-FU subjects experienced adverse events during the treatment period such as erythema (99%), scaling/dryness (95%), crusting (87%), pruritus (85%), stinging/burning (87%), edema (69%), and erosions (68%). There were no significant non-skin related adverse events demonstrated in the development program.

One death occurred in an 82 year old man of presumed cardiovascular causes and was not judged by the applicant or this reviewer to be related to study medication.

The applicant concluded that no serious adverse events in the phase 3 studies were related to study medication. This reviewer concurs with that conclusion. No significant differences in serious adverse events between the two active arms of study 048 were identified. No adverse events were reported that resembled any systemic allergy symptoms, or signs of anaphylaxis which is a theoretical concern due to the presence of (b) (4) peanut oil in the Tolak (fluorouracil) 4% formulation.

The common side effects of skin irritation, dryness, redness, edema, stinging/burning and peeling are predictable with this drug product and labeling is adequate to address these safety concerns.

Office of Surveillance and Epidemiology recommendations to add warnings for pancytopenia, eye irritation and conjunctivitis, and biopsy of lesions that did not respond to therapy will be included in adverse events product labeling.

The 048 study using the Efudex comparator arm demonstrated comparable safety. Local safety was assessed in all trials. While local safety was better with the Tolak (fluorouracil) Cream 4%, comparative claims will be limited since the Efudex comparator was a higher concentration of 5-FU and was administered twice per day as opposed to once per day for Tolak (fluorouracil) Cream. This reviewer concludes that the applicant has adequately established a systemic safety bridge for the application of Tolak (fluorouracil) Cream 4% and that systemic and local safety of the proposed Tolak (fluorouracil) Cream 4% is expected to be no worse than the profile of the comparator, Efudex Cream 5%.

1.3.4 Dosing Regimen and Administration

The applicant recommends that Tolak (fluorouracil) Cream 4% be applied once daily for four weeks. Treatment areas included only the face, and/or ears, and/or scalp in the phase 3 trials.

1.3.5 Drug-Drug Interactions

Drug-drug interaction studies were not performed.

1.3.6 Special Populations

The population studied averaged 68 years of age and correlates with the population affected with actinic keratoses. 99% of study subjects were white, correlating with the clinical observation that fair skinned persons have the highest incidence of actinic keratoses.

The applicant has submitted a full pediatric waiver request based on information that actinic keratoses grow slowly and typically require years to develop in reaction to photo-damaged skin and consequently rarely occur in children. A full waiver is recommended for the pediatric age group since the actinic lesions to be treated are extremely rare in children.

2. INTRODUCTION AND BACKGROUND

Actinic keratoses are lesions that begin in the epidermis in the sun-exposed areas of the body. The lesions appear as rough, scaly patches that range in color form normal skin tone to reddish brown. They are often circumscribed and are usually 1 mm to 2.5 cm in diameter. Patients may present with a single, well defined lesion, or multiple less defined lesions covering a large area of skin.

Lesions are most likely to develop in fair skinned persons living in sunny climates, and disease prevalence increases with age. It has been estimated that 75% of persons 80 years of age and older have actinic keratoses.

The lesions take years to develop and are more common in men than women. Persons with an extensive history of sun exposure are at greatest risk. More than 80 percent of actinic keratoses occur on areas of the skin with the most sun exposure such as the head, neck, forearms, and hands. Most lesions are asymptomatic, but some cause pruritus or burning.

Actinic keratoses are the most common pre-malignant lesions seen by dermatologists, and have the potential to progress to squamous cell carcinomas. Although most actinic keratoses do not progress to carcinomas, up to 60 percent of cutaneous squamous cell carcinomas arise from actinic keratoses.

5-Fluorouracil has been used for since 1957 as an antineoplastic agent administered by the parental (intravenous) route. 5-fluorouracil (5-FU), classified as a nucleoside metabolic inhibitor, is a pyrimidine analog that works against actinic keratosis (AK) lesions by competitively inhibiting the enzyme thymidylate synthetase, creating a thymine deficiency and resulting in inhibition of DNA synthesis and cytotoxicity.

2.1 Product Information

The applicant has submitted a 4% formulation of 5-fluorouracil cream, Tolak (fluorouracil) Cream 4%, for daily topical applications in the treatment of actinic keratoses of the face, scalp and ears.

Topical 5-fluorouracil (5-FU) cream has been used to treat actinic keratoses (AKs) since the early 1960s, and was first approved by the Agency in 1970. It acts by inhibiting DNA synthesis and hence inducing premature cell death. This effect is magnified in rapidly dividing tumor cells which generate larger amounts of DNA than their healthy counterparts.

Fluorouracil cream is currently available in concentrations ranging from 0.5% to 5%. Dosing is twice per day for two to four weeks. Fluorouracil therapy is used alone or in combination with other therapies such as treatment prior to cryosurgery for actinic lesions.

The sponsor has conducted a clinical study to form a clinical bridge for systemic safety to Efudex cream (5% 5-fluorouracil cream). Efudex (5-fluorouracil) cream, 5%, was approved for marketing in the US for the topical treatment of actinic or solar keratosis and superficial basal cell carcinomas on July 29, 1970. For the actinic keratosis indication, Efudex cream is applied twice daily to the affected area. The label states that medication should be continued until the inflammatory response reaches the erosion stage and then terminated. The usual duration of therapy for actinic keratosis is from 2 – 4 weeks. The label states that complete healing of the lesions may not be evident for 1 – 2 months following cessation of Efudex therapy.

Only the 5% strength of the Efudex cream or solution formulation is recommended for the treatment of superficial basal cell carcinoma. For the superficial basal cell carcinoma indication, Efudex cream is applied twice daily to the affected area. The duration of therapy is for at least 3 – 6 weeks. The label states that therapy may be required for as long as 10 – 12 weeks before the lesions are obliterated.

The applicant has completed assessments only for the treatment of actinic keratoses on the face, ears and scalp. Studies were not performed, and no application has been made, for the treatment of superficial basal cell carcinomas with Tolak Cream.

2.2 Currently Available Treatment for Indications

Actinic keratoses may be treated for cosmetic reasons, or for relief of associated symptoms, but the most compelling reason for treatment is to prevent the development of squamous cell carcinomas. Treatment options include ablative (destructive) therapies or topical therapies.

Cryosurgery using liquid nitrogen is the most common modality of treating actinic keratoses, although compressed nitrous oxide or carbon dioxide is also used. Liquid nitrogen is sprayed directly on the lesions or applied using a cotton-tipped applicator. Treatment success correlates with time of application.

Curettage involves mechanically scraping away abnormal tissue using a sharp curette, and requires local anesthesia. Electrosurgery is sometimes used in combination to destroy remaining tissue and to provide hemostasis.

Photodynamic therapy (PDT) involves applying a photosensitizing agent to each actinic lesion, followed by exposure to light of a specific wavelength. This leads to cell death of the treated tissue. Topical aminolevulinic acid, (Levulan Kerastick, DUSA Pharmaceuticals, Wilmington, MA) – PDT was approved by the FDA in December 1999 for actinic keratoses. A second photosensitizer, methyl- aminolevulinic acid (Metvixia, Galderma USA, Ft. Worth Texas), is FDA-approved for treatment of AKs in conjunction with a proprietary broadband red light when used in conjunction with lesion preparation (debridement), but it is not currently marketed.

Topical therapies include several alternatives beyond fluorouracil products. Imiquimod cream 5%, (Aldara) diclofenac gel 3%, (Solaraze) are approved for actinic keratoses. Topical tretinoin (Retin A, and others), salicylic acid, and alpha hydroxy acids are used for treatment, or as part of adjunctive treatment, but are not currently approved for this indication.

Dermabrasion, chemical peels, and laser therapy are also used by a limited number of providers, but none are approved for the actinic keratosis indication.

2.3 Availability of Proposed Active Ingredient in the United States

Fluorouracil was first approved as an injectable compound for adjunctive therapy in colon-rectal cancer in combination with leucovorin on April 25, 1962. It is also available in multiple strengths as an injectable product under multiple ANDA's.

5-Fluorouracil is available in concentrations ranging from 0.5% to 5%, in topical solutions and creams. Efudex cream was first approved on July 29, 1970 under NDA 16-831.

A history of marketed topical formulations includes:

Drug:	NDA #:	Initial Approval Date:
Carac Cream 0.5%	20-985	10/27/00
Fluoroplex Solution 1%	16-765	7/31/70 (now discontinued)
Fluoroplex Cream 1%	16-988	8/6/71
Efudex solution 2%	16-831	7/29/70
5-fluorouracil solution 2%	76-526	11/5/03
Efudex Cream, Solution 5%	16-831	7/29/70
Fluorouracil Solution 5%	76-526	11/5/03

2.4 Important Issues With Pharmacologically Related Products

Labeling contraindications will mirror those of the Efudex label, and include pregnancy category of X and use in patients with dihydropyrimidine dehydrogenase (DPH) deficiency.

The vehicle for this application includes (b) (4) peanut oil, and a labeling precaution has been recommended for caution in prescribing Tolak (fluorouracil) Cream to peanut sensitive individuals.

2.5 Presubmission Regulatory Activity

A pre-IND meeting was held on August 16, 2004. Concerns were expressed regarding the potential allergenicity of the (b) (4) peanut oil used in the formulation. Inclusion criteria were recommended to define the target lesions precisely to ensure that targeted AK lesions were not misdiagnosed squamous cell carcinoma lesions.

IND 69,841 was opened November 8, 2004 with a phase 2 dose ranging study.

An End of Phase 2 meeting was held on November 21, 2005. Pertinent discussion included the need to maintain blinding in the phase 3 trials since the proposed product was planned to be dosed once daily and the comparator product, Efudex 5% cream, is labeled for twice daily application.

Two phase 3 protocols were submitted in January, 2006 for Special Protocol Assessment.

Specific comments were conveyed regarding the protocols, and the Agency commented that one study with the new product demonstrating non-inferiority to the reference listed drug may be sufficient for approval. If non-inferiority was not demonstrated, the applicant would need to conduct another two arm trial to demonstrate superiority to vehicle.

A pre-NDA meeting was planned, but was cancelled in April, 2007, as the meeting responses were considered complete. The applicant was cautioned that the three arm study lacked pharmacokinetic data and did not successfully establish a bridge to the reference listed product, Efudex cream 5%:

> Study HD-FU3B-048 was of appropriate design to bridge to the listed drug, Efudex. Specifically, the study included the following arms: the sponsor's product, the sponsor's vehicle and the listed drug (Efudex). However, study HD-FU3B-048 does not sufficiently establish the bridge, as it does not provide for any pharmacokinetic data, and this is a critical piece to establishing the bridge (also see the clinical pharmacology/biopharmaceutics comments). The NDA should clearly identify which sections are intended to fulfill the elements of a 505(b)(2) application and articulate how, in the sponsor's opinion, the elements of a 505(b)(2) application have been fulfilled. Study HD-FU3S-049 was not designed to bridge to the listed drug, as this was a two-arm study in which the sponsor's product was compared to its vehicle.

The applicant was also informed that no additional long term studies would need to be conducted for the NDA, and a determination of what information might be needed in phase 4 would be made during the review process.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The composition of the 5 Fluorouracil cream 4% product in the submission is detailed in the following table:

Clinical Review Table 1
Formulation composition of 5 Fluorouracil 4% Cream

Ingredient	w/w%
5-Fluorouracil, USP	4.00
Butylated hydroxytoluene, NF	(b) (4)
Cetyl alcohol, NF	
Citric acid, USP	
Glycerin, USP	
(b) (4) (Arlacel 165)[a]	
Isopropyl myristate, NF	
Methyl gluceth-10[b]	
Methylparaben, NF	
Propylparaben, NF	
Purified water, USP	
(b) (4) peanut oil, NF[c]	
Sodium hydroxide, NF	
Stearic acid, NF	
Stearyl alcohol, NF	

(b) (4)

The sponsor stated that the (b) (4) peanut oil is (b) (4) Hill Dermaceuticals, Inc (b) (4). The sponsor states that the process by which the raw material is made has not differed from previous commitments, as stated by the supplier. (b) (4) .

The CMC review by Dr. Chang includes the following conclusion regarding the peanut protein content:

> "Protein content in (b) (4) peanut oil (b) (4) The proposed specification of (b) (4) peanut oil NF includes a test for protein content by amino acid analysis with a limit of NMT (b) (4) ppm. Analytical procedure for this test is poorly written and confusing and validation data are inadequate due to lack of accuracy, precision, linearity, etc. **Nevertheless, these issues are not critical as long as no labeling claim is made regarding the level of protein content."**

Reviewer comment: The adequacy of the process to minimize the peanut allergens in the (b) (4) *peanut oil is under ongoing review in ONDQA.*

There were no adverse reaction reports that suggested that peanut oil was implicated. The signs of local allergy (redness, swelling, and peeling) are similar to what could be expected from routine use of the 5-FU product for the desired indication. Thus local allergy would be impossible to distinguish. The "anaphylactoid reaction" which occurred in one 66 year old male described in section 7.1.6 of this clinical review, the only systemic adverse event that could be categorized as "allergic reaction", seems unlikely to be caused by Ig E mediated allergy. This "anaphylactoid reaction" is recommended to be deleted from the proposed product labeling since it is very unlikely related to a systemic allergic reaction.

Labeling which is similar (b) (4) *should be included, since while the risk for this topical product is minimal, it is not zero. The following is suggested (labeling negotiations are underway at the time of this review):*

5.5 Hypersensitivity, including Use in Peanut-Sensitive Individuals

TOLAK Hypersensitivity reactions have been noted for topical fluorouracil drugs.
Physicians should use caution in prescribing TOLAK Cream for peanut-sensitive individuals since TOLAK Cream contains (b) (4) peanut oil NF. TOLAK Cream should be discontinued immediately and appropriate therapy instituted if signs of severe hypersensitivity occur.

Dr. Chang also comments in the CMC review that data are insufficient to support the proposed shelf life of (b) (4) months. The recommended shelf life is 15 months pre ICH Q1E guidelines, and the storage temperature for the drug product is maintenance at 25º C (77 º F), with excursion permitted to 15º – 30º C (59º -86º F) (b) (4) These are reflected in the product labeling.

The Office of Compliance recommendations and facility inspections of Hill Dermaceuticals facilities are pending at the time of this review.

3.2 Animal Pharmacology/Toxicology

The sponsor is relying on literature studies to fulfill the nonclinical toxicology data needs for this 505(b)(2) application. No nonclinical toxicology or safety pharmacology studies were conducted to support this NDA submission. The sponsor included literature references that address the toxicology and safety pharmacology of 5-fluorouracil.

The Division has determined that the treatment of actinic keratosis with 5-fluorouracil is not a chronic indication. Even though there may be recurrence of actinic keratosis lesions

in the same patient, these patients would often be treated with a different therapy than that used to treat the original lesions. Therefore, the need for carcinogenicity studies is waived for the 4% 5- fluorouracil cream.

Based on the profile established for 5-fluorouracil in the literature, no safety pharmacology studies, nonclinical pharmacokinetic studies, reproductive, developmental toxicology, or genetic toxicology studies were recommended for the 4% 5-fluorouracil cream by the Pharmacology/Toxicology review team.

The Pharmacology/Toxicology review concludes, "The 4% 5-fluorouracil cream NDA is a 505(b)(2) submission since the sponsor generated a clinical systemic safety bridge to Efudex cream which allows the Agency to use our findings of safety to support the 4% 5-fluorouracil cream drug product. The nonclinical information contained in the Efudex cream label will be incorporated into the 4% 5-fluorouracil cream label. No additional nonclinical toxicology studies are recommended for the 4% 5-fluorouracil drug product."

Reviewer comment: The clinical reviewer agrees that the literature support for non-clinical information, along with the systemic PK information compared with Efudex, the reference listed drug, is sufficient for bridging to the Agency's findings regarding Efudex. Efficacy is demonstrated by the two pivotal clinical phase 3 studies, 048 and 049, reviewed in section 6 of this review. Bridging for safety is accomplished by the comparison study 048 and relevant pharmacokinetic data.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources of clinical data for this review included the original submission for NDA 22-259, and additional efficacy and safety information submitted at the request of the Division during the review process.

The applicant conducted seven clinical studies from which adverse event and clinical efficacy data was collected: three phase 1 safety studies in healthy subjects, two phase 2 trials to assess dose ranging and pharmacokinetic parameters, and two phase 3 trials to prove safety and efficacy.

The phase 1 trials studied the photoallergy potential after exposure to ultraviolet (UV) radiation (HD-FU1206PA); the phototoxic potential after UV radiation exposure compared to vehicle or a blank patch (HD-FU1106PT); and contact sensitization compared to an active control of Efudex Cream 5%, an inactive control of product vehicle, and an inactive control of aqueous sodium chloride (0.9%) (PRACS R05-1393).

The phase 2 dose ranging study (HD-FUDR-045) compared the safety and efficacy of two durations (2 weeks vs. 4 weeks) and frequencies of dosing (once daily vs. twice daily) with Tolak (fluorouracil) cream 4% in comparison to each other and also to an active control (Efudex Cream 5% twice daily for 4 weeks) and to an inactive control (vehicle cream).

Another phase 2 study (HD-FU1206SA) compared pharmacokinetic parameters of Tolak (fluorouracil) Cream 4% to Efudex Cream 5% in subjects with AK.

Two phase 3 trials were conducted in support of the NDA. HD-FUP3B-048 was designed to evaluate the efficacy and safety of once daily application over four weeks of Tolak (fluorouracil) Cream 4% compared with four week applications of twice daily applications of Efudex 5% cream, Efudex vehicle, and Tolak (fluorouracil) vehicle. HP-FU3S-049 was designed to evaluate the efficacy and safety of once daily application of Tolak (fluorouracil) Cream 4% compared with Tolak (fluorouracil) vehicle.

A phase 4 long term safety study (HD-FUP4LTS-050) which includes subjects from the 048 and 049 phase 3 studies is ongoing. The planned number of subjects is 400, and will evaluate the recurrence rates and long term safety in subjects treated with Tolak (fluorouracil) Cream 4%.

4.2 Tables of Clinical Studies

Clinical Review Table 2
Clinical Studies for Tolak (fluorouracil) Cream 4%

Study No.	Study Design	Study Population	Study Drug, Dose, and Frequency	No. Subjects	Duration of Drug Treatment	Completion Status / Location of Report
Controlled Phase III Primary Efficacy Studies in AK						
HD-FUP3B-048	Phase III, randomized, investigator- blind, 4-arm, parallel group efficacy and safety study	Subjects ≥18 years, with AK of the face and/or ears and/or scalp	4% TRADENAME cream QD	353	4 weeks	Complete / Module 5.3.5.1
			TRADENAME vehicle cream QD	70		
			Efudex® 5% cream BID	349		
			Comparator vehicle cream BID	69		
HD-FUP3S-049	Phase III, randomized, double-blind, 2-arm, parallel group safety and efficacy study	Subjects ≥18 years, with AK of the face and/or ears and/or scalp	4% TRADENAME cream QD	50	4 weeks	Complete / Module 5.3.5.1
			TRADENAME vehicle cream QD	50		
Controlled Phase II Dose Ranging Study in AK						
HD-FUDR-045	Phase II, randomized, investigator-blind, 6-arm, parallel group safety and efficacy study	Subjects ≥18 years, with AK of the face and/or ears and/or scalp	4% TRADENAME Cream QD	20	4 weeks	Complete / Module 5.3.5.1
			4% TRADENAME Cream BID	20	4 weeks	
			4%TRADENAME Cream QD	20	2 weeks	
			4% TRADENAME Cream BID	21	2 weeks	
			TRADENAME Vehicle Cream BID	20	4 weeks	
			Efudex 5% Cream BID	20	4 weeks	
Controlled Phase II Pharmacokinetic Study in AK						
HD-FU1206SA	Phase II, randomized, open-label, parallel group pharmacokinetic and safety study	Subjects ≥18 years, with AK of the face and/or ears and/or scalp	4% TRADENAME cream QD	21	4 weeks	Complete / Module 5.3.3.2 (Data Listings)
			Efudex 5% cream BID	22		
Controlled Phase I Special Safety Studies in Healthy Subjects						
HD-FU1106PT	Phase I, randomized, double-blind safety study of the phototoxic potential of 4% TRADENAME cream	Healthy subjects 18-65 years with Fitzpatrick Skin Type I, II, or III	4% TRADENAME Cream patch	33	One 24-hour application	Complete / Module 5.3.4.1
			TRADENAME Vehicle Cream patch			
			Blank patch			
HD-FU1206PA	Phase I, randomized, double-blind safety study of the photoallergy potential of 4%	Healthy subjects 18-65 years with Fitzpatrick Skin Type I, II, or III	4% TRADENAME Cream patch	60	Six 24-hour induction applications,	Complete / Module 5.3.4.1
	TRADENAME cream		TRADENAME Vehicle Cream patch			
			Blank patch		then single 24-hour application to naïve site	
PRACS R05-1393	Phase I, randomized, double-blind safety study of the contact sensitization induction potential of 4% TRADENAME cream	Healthy subjects 18-65 years	4% TRADENAME Cream patch	231	Nine applications every 48-72 hours, then single 48-hour application to naïve site	Complete / Module 5.3.4.1
			Efudex 5% Cream patch			
			TRADENAME Cream Vehicle patch			
			Aqueous sodium chloride 0.9% patch			
Phase IV Long-Term Study						
HD-FUP4LTS-050	Phase IV extension study of HD-FUP3B-048 and HD-FUP3S-049 to evaluate recurrence rates and long-term safety of 4% TRADENAME cream	Subjects from Studies HD-FUP3B-048 and HD-FUP3S-049	4% TRADENAME Cream QD	400 planned	If retreated, 4 weeks	Ongoing / No Report Available

4.3 Review Strategy

Adverse event data was reviewed for all seven completed studies through all three phases of development. Efficacy data was reviewed for the two phase 3 studies. Complete study data from the long term 050 study has not yet been submitted for review. A synopsis of study results for the long term study was submitted in March, 2008 in the safety update and is discussed in section 7.2.9 of this clinical review.

The Office of Surveillance and Epidemiology conducted two related reviews in March, 2008. A post-marketing analysis of all adverse events was conducted by the Division of Adverse Event Analysis I in relation to Carac Cream 0.5%, NDA 20-985, (with additional reports regarding Efudex, NDA 16-831, and Fluoroplex, NDA 16-765, products) examined 986 reports. A separate analysis, from the OSE Division of Epidemiology, examined a phase 4 study report regarding additional safety data requested for Carac Cream, 0.5%. These consultation reports are discussed in Section 8.8 of this clinical review.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was requested to examine sites 003 in study 049 and 011 and 022 in study 048. In 048, Site 022 was selected as having the second largest enrollment (59 subjects) and one of the largest treatment effects. Site 011 also had one of the largest enrollments (48 subjects) but review of the data from this site suggested that lesion count assessment did not follow the expected pattern of short term increase in erythema scores.

In 049, site 003 was the second largest site by enrollment (24 subjects) and overall efficacy appears to be lower than other sites.

No specific safety concerns were referred to DSI bases on preliminary review of the data.

The DSI inspection reports are pending as of the date of this review.

In addition, the applicant's analyses were reviewed, and independent analyses were performed by the Agency biostatistics reviewer.

4.5 Compliance with Good Clinical Practices

The applicant affirmed, in an amendment dated November 19, 2007, that the studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP). All subjects were informed about the study and provided the opportunity to ask questions. Subjects, or their legal representatives, read, signed, and dated the IRB-approved consent form before taking part in any study activity.

4.6 Financial Disclosures

The applicant certified in Form 3454 that they had not entered into any financial arrangements with any of the clinical investigators. It was also affirmed that none of the clinical investigators disclosed any proprietary interest in the product, or significant equity interest in the sponsor company. Certification was made that no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

5. CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Study HD-FU1206SA was undertaken to compare the steady state plasma concentration of 5-fluorouracil after application of Tolak (fluorouracil) Cream 4% with Efudex in subjects with actinic keratoses. Overall systemic absorption was low, with 8 of 21 subjects (38%) treated with Tolak (fluorouracil) and 11 of 22 subjects (50%) treated with Efudex having undetectable levels of plasma 5-FU at all sampling time points.

Systemic exposure appeared to be similar in subjects treated with Tolak (fluorouracil) as compared with Efudex as differences in Cmax and Tmax were small.

Adverse events were uncommon and almost all were related to application site reactions in both treatment groups. These are discussed further in section 7, Integrated Review of Safety.

Reviewer comment: This pharmacokinetic study is an important facet of the 505(b)(2) application since the systemic PK data compared with Efudex is the systemic safety bridge. In combination with the literature support for the non-clinical requirements, the bridge is acceptable for this application, since two pivotal studies (048 and 049) are the basis of clinical efficacy demonstration.

The clinical pharmacology review has not been finalized as of the date of this review.

6. INTEGRATED REVIEW OF EFFICACY

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.

6.1 Indication

The indication sought by the applicant is for the topical treatment of actinic keratosis lesions of the face, ears and scalp.

Reviewer comment: The labels for Efudex, the reference listed comparator product, and Fluoroplex 1% topical cream have no site specific references in the approved indications. Carac Cream 0.5% has a stated indication for "topical treatment of multiple actinic or solar keratoses of the face and anterior scalp."

6.1.2 General Discussion of Endpoints

Two phase 3 studies were conducted in support of the efficacy of Tolak (fluorouracil) Cream 4% in the topical treatment of actinic keratosis.

Study HD-FUP3B-048 (study 048) was designed to establish the safety and efficacy of once daily application over four weeks of Tolak (fluorouracil) Cream 4% compared with four week applications of:

--Twice daily applications of Efudex Cream 5%;
--Once daily applications of Tolak (fluorouracil) vehicle dream; and
--Twice daily applications of Efudex vehicle cream.

The applicant claims to establish a clinical bridge suitable to meet the requirements for a submission under Section 505(b)(2) in this study. The stated goal was to demonstrate non-

inferiority of Tolak (fluorouracil) Cream 4% to the Efudex Cream 5% and superiority to the Tolak (fluorouracil) vehicle.

However, while this study 048 demonstrated superiority of Tolak (fluorouracil) Cream 4% to its vehicle, it failed to demonstrate non-inferiority to Efudex Cream 5% as the 97.5% lower confidence bounds for the treatment difference were -11.1% (ITT) and -12.8% (PP) with a pre-specified non-inferiority margin of (b)(4)%. A second study was conducted as the second well controlled trial to demonstrated superiority of Tolak (fluorouracil) Cream 4% to vehicle.

This study was HD-FUP3S-049 (study 049), and enrolled 100 subjects across six study centers in the United States. This trial compared once daily applications of Tolak (fluorouracil) Cream 4% for four weeks to vehicle cream applied once daily for four weeks. Subjects applied the study medication to the face, ears and scalp as directed for four weeks. Subjects returned for assessments at weeks 1, 2, and 4 and for two post-treatment visits (2 and 4 weeks off treatment.)

The primary efficacy endpoint in both phase 3 studies was the proportion of subjects with complete clearing of all actinic keratosis lesions at four weeks off treatment, in the ITT population. The time point of four weeks post-treatment was chosen to allow local adverse events from the study medication to subside.

Secondary endpoints in the phase 3 studies included:

1. The proportion of subjects in whom 75% of AK lesions have cleared at four weeks off treatment; and
2. The percentage change in the number of AK lesions from baseline assessed at four weeks off treatment.

These endpoints were the same as submitted in the Special Protocol Assessment submissions to IND 69,841 on January 3, 2006.

6.1.3 Study Design

Study 048 was conducted to demonstrate non-inferiority of Tolak (fluorouracil) Cream 4% to the Efudex Cream 5% and superiority to the Tolak (fluorouracil) vehicle. Study 048 was conducted from March 30, 2006 to December 29, 2006.

The study enrolled 841 subjects (353 to 4% 5-FU, 349 to Efudex, 70 to vehicle once daily, and 69 to vehicle twice daily) at 26 U.S. centers. Subjects were selected based on the following eligibility criteria:

Inclusion Criteria:

1. Subject has completed and signed an appropriately administered Institutional Review Board approved informed consent form prior to any study related procedures.
2. Subject is at least 18 years old of either gender.
3. Subject is willing and able to apply the assigned study medication as directed and comply with required visits for the duration of the study.
4. Subject has a clinical diagnosis of actinic keratosis (AK).
5. Subject has 5 or more previously untreated clinically recognizable (palpable and/or visible to unaided eye) AK lesions of the face, and/or ears and/or scalp; and at least 5 AK lesions are greater than or equal to 4 mm in longest diameter. The AK lesions were clinically typical non-hypertrophic and/or non-hyperkeratotic. None of the AK lesions should exceed 1 cm in size.
6. Subject is in good general condition and free of any disease state or condition which, in the investigator's opinion, might impair evaluation of actinic keratosis or expose the subject to an unacceptable risk by study participation.
7. Females of childbearing potential (a) must have a negative urine pregnancy test (b) and agree to use an effective form of birth control for the duration of the study (e.g.: stabilized on oral contraceptives for at least one month, implant, injection, transdermal, IUD, condom and spermicide, or diaphragm and spermicide).

[a] Females of Child Bearing Potential (FOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months). Females who are using oral, implanted or, injectable contraceptive hormones, an intrauterine device (IUD), barrier methods (diaphragm, condoms, spermicide) to prevent pregnancy, practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential.

[b] Urine pregnancy tests must have a minimum sensitivity of 25-mIU ß-HCG/ml of urine and must be performed within 72 hours prior to the start of study medication.

Exclusion Criteria:

1. Subject has AK lesions within treatment areas which are hyperkeratotic or which are clinically suspected to be squamous cell carcinoma (SCC).
2. Subject has used 5-fluorouracil or any systemic cancer treatment within two months prior to the study.
3. Subject has used any other AK treatments or therapies (e.g., cryotherapy or photodynamic therapy) in the treatment area(s) within two months prior to starting the study.
4. Subject has used any systemic steroids, immunosuppressants or immunomodulators within one month prior to the study.
5. Subject has used prescription retinoids or topical steroids in the treatment area(s) within one month prior to the study.
6. Subject has used glycolic acid products, alpha-hydroxy products in the treatment area(s) within one month prior to starting the study, or chemical peeling products within two months prior to starting the study.
7. Subject has a history of sensitivity to any of the ingredients in the study medications.
8. Subject is pregnant or a nursing mother.

9. Subject is currently participating, or has participated in the 30 days prior to the study, in an investigational study.

Clinical Review Table 3
Study 048 Flowchart

Study Day (Phase)	Baseline (Enrollment)	Week 1 (±3 days)	Week 2 (±3 days)	Week 4 (End of treatment) (±3 days)	Week 6 (2 wks off treatment) (±3 days)	Week 8 (4 wks off treatment) (±5 days)
Visit	1 (Day 0)	2 (Day 7)	3 (Day 14)	4 (Day 28)	5 (Day 42)	6 (Day 56)
Inclusion/ Exclusion criteria	X					
Informed consent	X					
Medical history & demographics	X					
Urine pregnancy test (as required)	X			X		
Collect laboratory samples[a]	X			X		
Clinical Evaluation	X	X	X	X	X	X
Study medication application	⟷	⟷	⟷	⟷		
Report concomitant therapies	X	X	X	X	X	X
Report adverse events	X	X	X	X	X	X

[a] At selected study sites

Study 049 was conducted to provide a second adequate and well-controlled study to demonstrate superiority of Tolak (fluorouracil) Cream 4% to vehicle. No active comparator arm was included in this second phase 3 study. This was a randomized, double blind, vehicle-controlled multi-center trial. 100 subjects were enrolled across 6 study sites. Study 049 was conducted from May 22, 2006 to October 17, 2006.

Inclusion and Exclusion eligibility criteria were the same as listed in study 048 above. The study enrolled 100 subjects (50 to 4% 5-FU and 50 to vehicle) at 5 U.S. centers. The study 049 flowchart follows:

Clinical Review Table 4
Study 049 Flowchart

Study Day (Phase)	Baseline (Enrollment)	Week 1	Week 2	Week 4 (End of treatment)	Week 6 (2 wks off treatment)	Week 8 (4 wks off treatment)
Visit	1 (Day 0)	2 (Day 7)	3 (Day 14)	4 (Day 28)	5 (Day 42)	6 (Day 56)
Inclusion/ Exclusion criteria	X					
Informed consent	X					
Medical history & demographics	X					
Urine pregnancy test (as required)	X			X		
Clinical Evaluation	X	X	X	X	X	X
Study medication application	⟷					
Report concomitant therapies	X	X	X	X	X	X
Report adverse events	X	X	X	X	X	X

Reviewer comment: The applicant submitted both protocols for the 048 and 049 studies for special protocol assessment (SPA) at the same time to IND 69,841 on January 3, 2006. Study 049 originally included a [redacted] (b) (4) *but that plan was abandoned by the applicant prior to initiating the study.*

The Applicant may have anticipated that non-inferiority may have been difficult to demonstrate and submitted the two protocols for SPA and conducted both concurrently. Thus, if the first study was unable to demonstrate the non-inferiority of the test product to the reference product, then the sponsor had the ability to demonstrate that the test product was superior to vehicle in two studies.

The data from the Efudex comparator arm, which uses a higher concentration of 5-FU at twice daily applications should not be used by the applicant to make comparative efficacy or safety claims.

Baseline Characteristics:

The demographics were well-balanced across the treatment arms in Study 048. In Study 049, which enrolled only 100 subjects, had some imbalances with regard to gender and baseline lesion counts. The mean age of subjects was around 67 years and about 80% of the subjects were male in both studies. In Study 049, of the 15 female subjects, 11 were randomized to 5-FU while only 4 were randomized to vehicle. About 4% of the subjects in Study 048 were Latino, although none of the subjects in Study 049 were. Nearly all of the subjects were white.

Clinical Review Table 5
Baseline Demographics—Study 048

	4% 5-FU N=353	Efudex N=349	Vehicle QD N=70	Vehicle BID N=69
Age (years)				
Mean	67.7	67.4	68.0	69.1
Range	36 - 88	37 - 94	47 - 84	37 - 88
Gender				
Male	287 (81%)	282 (81%)	58 (83%)	55 (80%)
Female	66 (19%)	67 (19%)	12 (17%)	14 (20%)
Ethnicity				
Hispanic/Latino	15 (4%)	17 (5%)	1 (1%)	3 (4%)
Not Hisp/Latino	338 (96%)	332 (95%)	69 (99%)	66 (96%)
Race				
White	348 (99%)	347 (99%)	70 (100%)	69 (100%)
Am. Ind./AK Native	1 (<1%)	-	-	-
Other	4 (1%)	2 (1%)	-	-
Lesions				
Mean	14.4	14.8	16.2	14.7
Range	5 - 82	5 - 76	5 - 90	5 - 49

Clinical Review Table 6
Baseline Demographics—Study 049

	4% 5-FU N=50	Vehicle N=50
Age (years)		
Mean	67.9	66.9
Range	44-85	33-87
Gender		
Male	39 (78%)	46 (92%)
Female	11 (22%)	4 (8%)
Ethnicity		
Not Hisp/Latino	50 (100%)	50 (100%)
Race		
White	50 (100%)	50 (100%)
Lesions		
Mean	19.2	23.2
Range	5 - 83	6 - 80

Reviewer comment: The age and racial makeup of the study populations for the phase 3

trials mirror the population seen clinically for the indication of actinic keratoses. These lesions show increasingly frequency with age and are uncommon in persons under 30 and are quite rate in African Americans and other deeply pigmented individuals.

6.1.4 Efficacy Findings

Tolak (fluorouracil) cream 4% was superior to its vehicle in the treatment of actinic keratoses in the two studies, 048 and 049, and these findings are the basis of demonstrating efficacy in this 505 (b)(2) application.

The test product was not shown to be non-inferior to the listed drug Efudex (97.5% lower confidence bounds of -11.1% (ITT) and -12.8% (PP) with a pre-specified non-inferiority margin of (b)(4)%) in Study 048.

Tolak (fluorouracil) cream 4% was also superior to its vehicle for the two secondary endpoints of the proportion with at least 75% clearance and the percent reduction in lesions at 4 weeks post-treatment.

Clinical Review Table 7
Efficacy Results, ITT Population—Study 048

	4% 5-FU	Efudex	Vehicle QD	Vehicle BID	p-value / LCB
	N=353	N=349	N=70	N=69	
Baseline Count (Mean)	14.4	14.8	16.2	14.7	
End of Study Count (Mean)	2.4	2.6	13.9	11.6	
Percent Reduction (Mean)	81.2%	80.0%	17.7%	20.2%	<0.001[a] -5.0%[b]
75% Clearance	284 (80%)	280 (80%)	5 (7%)	7 (10%)	<0.001[c] -5.9%[d]
Primary Endpoint: 100% Clearance	192 (54%)	202 (58%)	3 (4%)	3 (4%)	<0.001[c] -11.1%[d]

[a] Treatment p-value for 4% 5-FU vs. vehicle based on an ANOVA with factors for treatment and grouped investigator, limited to 4% 5-FU and vehicle groups
[b] 97.5% lower confidence bound for 4% 5-FU vs. Efudex based on an ANOVA with factors for treatment and grouped investigator, limited to 4% 5-FU and Efudex groups
[c] P-value for 4% 5-FU vs. vehicle based on a CMH test stratified by grouped investigator
[d] 97.% lower confidence bound for 4% 5-FU vs. Efudex based on Wald's confidence interval with Yate's continuity correction

Clinical Review Table 8
Efficacy Results, ITT Population—Study 049

	4% 5-FU	Vehicle	p-value
	N=50	N=50	
Baseline Count (Mean)	19.2	23.2	
End of Study Count (Mean)	7.1	21.7	
Percent Reduction (Mean)	56.9%	4.3%	<0.001
75% Clearance	37 (74%)	5 (10%)	<0.001
Primary Endpoint: 100% Clearance	12 (24%)	2 (4%)	0.004

As will be discussed in section 7.1.3 below, there were few subjects who completely discontinued from the study and most of these were due to subject decision to withdraw. Due to the application site irritation of Tolak (fluorouracil) Cream 4% and Efudex Cream 5%, some subjects did not complete the full treatment regimen. This number was 13-15% of the subjects in the Tolak (fluorouracil) Cream arms in the two phase 3 trials.

These subjects were assessed by Dr. Fritsch in her Agency Biostatistical analysis with regard to the impact of the length of treatment on the final clearance assessment. The expected number of treatment days was 28. The groupings were selected to roughly correspond to one week intervals. In Study 048, subjects who had at least 12 days of treatment had similar success rates to those who completed the study, while subjects with less than 12 days of treatment had lower success rates. In Study 049, the number of subjects who did not complete treatment is too small to make any meaningful comparisons.

Clinical Review Table 9
100% Clearance Rates by Number of Days Treated—Study 048

	4% 5-FU	Efudex	Vehicle QD	Vehicle BID
< 12 Days	2/10 (20%)	1/11 (9%)	0/1 (0%)	0/2 (0%)
12 – 20 Days	10/20 (50%)	28/41 (68%)	-	-
21 – 25 Days	14/28 (50%)	18/29 (62%)	0/1 (0%)	-
> 25 Days	166/288 (58%)	154/256 (60%)	3/68 (4%)	3/63 (5%)
Missing Days	0/7 (0%)	1/12 (8%)	-	0/4 (0%)

Clinical Review Table 10
100% Clearance Rates by Number of Days Treated—Study 049

	4% 5-FU	Vehicle
< 12 Days	1/5 (20%)	0/1 (0%)
12 – 20 Days	0/5 (0%)	0/1 (0%)
21 – 25 Days	1/3 (33%)	0/1 (0%)
> 25 Days	10/35 (29%)	2/47 (4%)
Missing Days	0/2 (0%)	-

No significant efficacy differences were noted in gender, or age subgroups. Nearly all the enrolled subjects (>99%) were white so analyses by race are not informative. Subjects can be classified by Fitzpatrick skin type. No significant differences in efficacy were noted by skin type.

The Biostatistics reviewer, Dr. Fritsch, points out that the clearance rate for 4% 5-FU was higher in Study 048 than 049 (54% vs. 24%). The reason for this difference is not clear, but analyses of differences in mean baseline lesion count and sample size between the two phase 3 studies do not seem to explain the differences.

The mean baseline lesion count in Study 049 was higher than in Study 048 (19.2 vs. 14.4). The baseline lesion count impacts the final number of lesions only when the baseline count is greater than about 20 to 25 lesions, which was not common in either study.

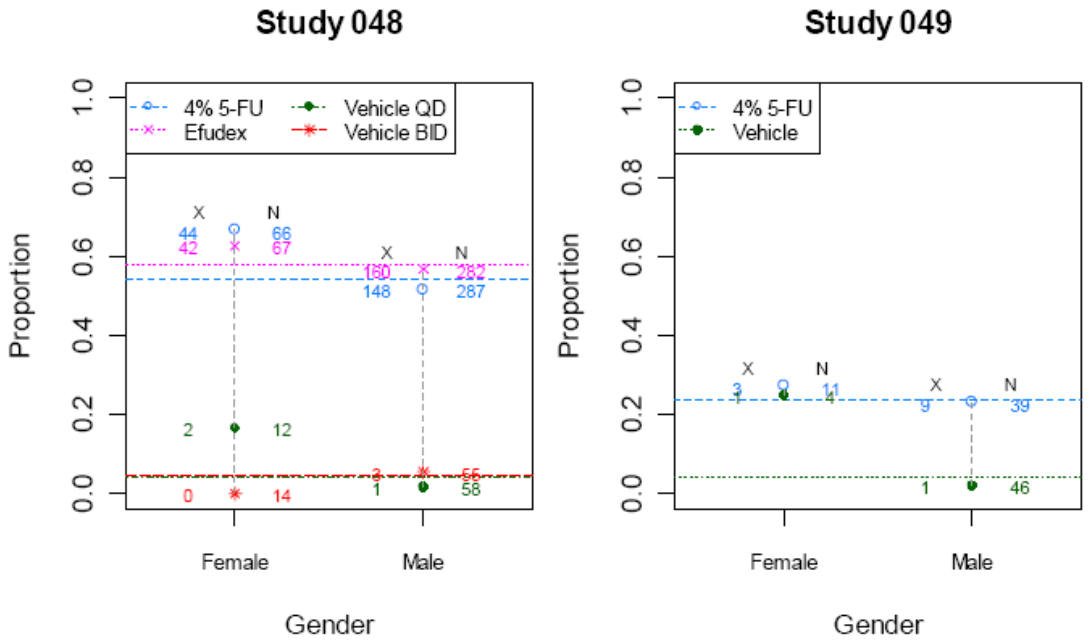
Since Study 048 enrolled 7 times as many 4% 5-FU subjects as Study 049, the estimates in Study 049 could have been less reliable. But since the Agency calculated confidence intervals for the two studies do not overlap, the lower level of precision associated with the estimate from the second study is unlikely to be the only reason that that study has a much smaller clearance rate estimate than the first study.

The Agency Biostatistical analyses demonstrate that the differing efficacy rates for 4% 5-FU in Studies 048 and 049 can also not be completely explained by differences in baseline lesion counts, nor from the differences in sample size. Thus, the differing response rates between the two studies may be due some other unidentified difference in the study subjects or other unidentified differences in how the studies were conducted.

Efficacy Results—Effects of Gender, Race and Age

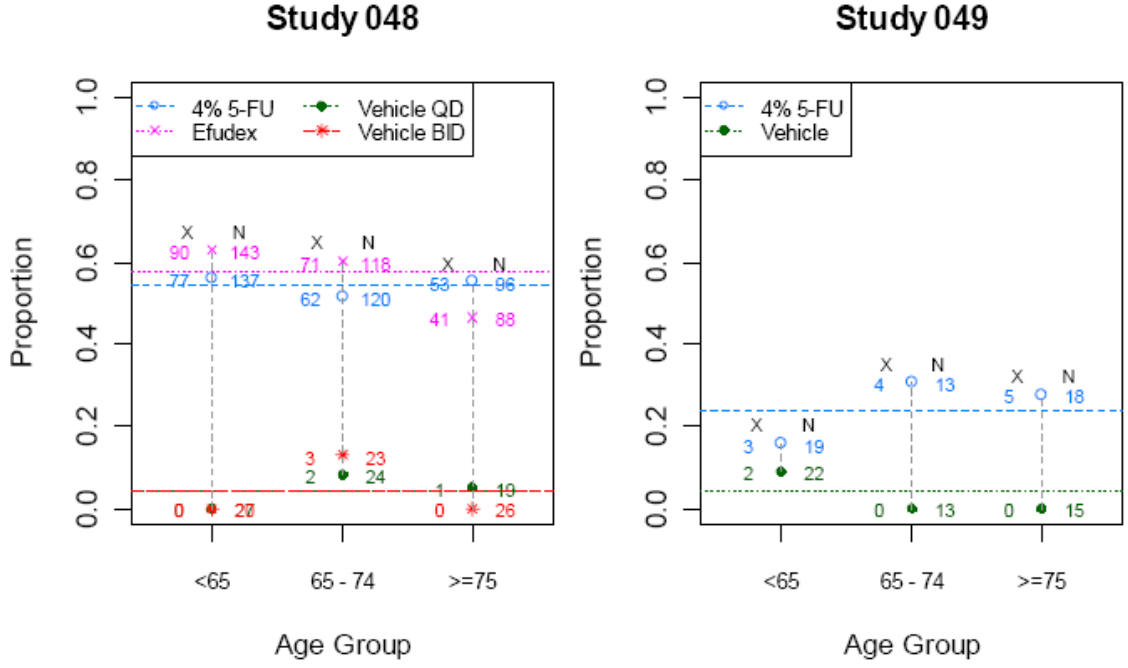
The studies were not powered to detect differences in subgroups; however, no obvious efficacy differences were noted in gender or age subgroups. Nearly all the enrolled subjects (>99%) were white so analyses by race are not informative.

Clinical Review Table 11
Lesion Clearance Rates by Gender



Note: X = Number cleared, N = Subgroup size

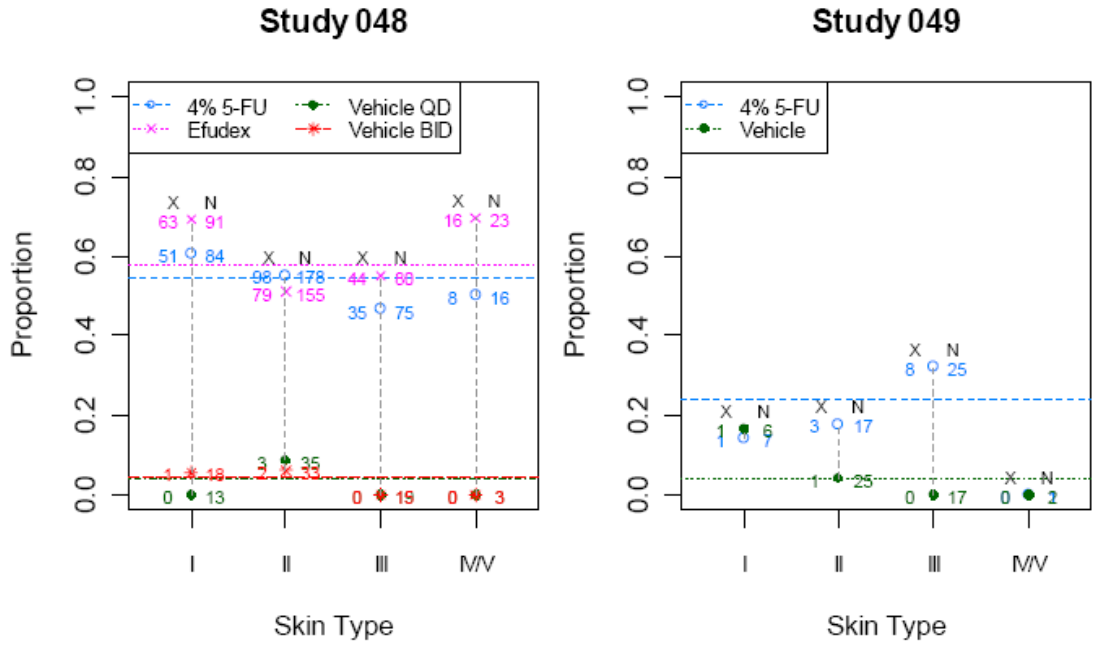
Clinical Review Table 12
Lesion Clearance Rates by Age Group



Note: X = Number cleared, N = Subgroup size

Nearly all (99%) subjects were white, but subjects were assessed by Fitzpatrick skin type. No obvious differences were noted by skin type.

Clinical Review Table 13
Lesion Clearance by Fitzpatrick Skin Type



Note: X = Number cleared, N = Subgroup size

6.1.5 Clinical Microbiology

The sponsor is not seeking an antimicrobial claim, and no clinical microbiology data was collected in the development program. 5-Fluorouracil has no known antimicrobial effects.

6.1.6 Efficacy Conclusions

Tolak (fluorouracil) Cream 4% demonstrated superiority over vehicle in both phase 3 studies across the primary, as well as secondary, pre-specified endpoints. Study 048 failed in its goal to demonstrate non-inferiority to Efudex Cream 5%, and the second study, 049, was used as the second study which confirmed superiority to vehicle. The Efudex arm in 048 will be used as a comparator for safety.

However, the treatment effect for the clearance rate was much higher in Study 048 than 049 (Study 048: 54% vs. 4%; Study 049: 24% vs. 4%). The reason for this difference is not clear, though it does not appear to be explained solely by differences in precision afforded by the respective sample sizes (Study 048 enrolled 353 Tolak (fluorouracil) Cream subjects while Study 049 enrolled 50 Tolak (fluorouracil) Cream subjects), or by differences in baseline lesion count (mean of 19.2 for Study 049 vs. 14.4 for Study 048 for 4% 5-FU subjects).

Reviewer comment: Since the initial 048 study failed to demonstrate non-inferiority to Efudex Cream 5%, data for this arm was not recommended for the Clinical Studies section of the product labeling. The applicant has submitted the results of superiority of its product over placebo and that information is recommended to be included in the label. Similarly, the Adverse Reaction section should only include the common, selected adverse events for the applicant's 5-fluorouracil product and vehicle. Comparisons to the third arm of the 048 study, which included Efudex Cream 5% at a higher concentration of 5-fluorouracil, at twice the daily dosage, would not be informative and allow the applicant to formulate marketing claims that were not assessed in the second phase 3 trial.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The applicant conducted seven clinical studies from which adverse event and other safety data was collected: three phase 1 safety studies in healthy subjects, two phase 2 trials to assess dose ranging and pharmacokinetic parameters, and two phase 3 trials to evaluate safety and efficacy.

829 subjects were exposed to Tolak (fluorouracil) Cream 4% in the applicant's development program. Phase 4 subjects are not included since the final study report has not yet been submitted.

Clinical Review Table 14
Summary of Subjects in All Studies Evaluating Safety in Humans

Study Number	4% TRADE-NAME Cream	TRADE-NAME Vehicle Cream	Efudex® 5% Cream	Other Vehicle Cream[1]	Total
Primary Clinical Studies[2]					
HD-FUP3B-048	353	70	349	69	841
HD-FUP3S-049	50	50	NA	NA	100
Supporting Clinical Study					
HD-FUDR-045	81[3]	20	20	NA	121
Pharmacokinetic Study[2]					
HD-FU1206SA	21	NA	22	NA	43
Special Safety Studies					
HD-FU1106PT[4]	33	33	NA	NA	33
HD-FU1206PA[4]	60	60	NA	NA	60
PRACS R05-1393[4]	231	231	231	NA	231
Long-Term Study					
HD-FUP4LTS-050[5]	NA	NA	NA	NA	NA
Total	829	140	391	69	1429

NA=not available or not applicable

1. Comparator cream twice per day, used for blinding for comparisons with Efudex
2. Subjects in the 4% TRADENAME Cream QD group received TRADENAME Cream QD for up to 4 weeks
3. 20 subjects received TRADENAME Cream QD for 4 weeks, 20 subjects received TRADENAME Cream BID for 4 weeks, 20 subjects received TRADENAME Cream QD for 2 weeks, and 21 subjects received TRADENAME Cream BID for 2 weeks
4. All subjects received all medications and are tallied only in the 4% TRADENAME column
5. Study is ongoing; no data are available

7.1.1 Deaths

One death occurred during phase 3 Study 049. Subject 2-73 was an 82 year old man with a history of hypertension, hypercholesterolemia, and quadruple bypass surgery who died at home of a presumptive heart attack one (b) (6) after study enrollment. He had been randomized into the Tolak (fluorouracil) Cream 4% arm of the study and had completed the dosing phase prior to his death. No autopsy confirmation of cause of death was performed.

Local adverse event data for this subject is provided in the following table:

Clinical Review Table 15
Data for Study 049--Subject 2-73 (who died following treatment)

Visit	1	2	3	4	5	6
Visit Date	10AUG06	16AUG06	28AUG06	07SEP06	-	-
Days from Baseline	0	6	18	28	-	-
Lesions	18	51	87	123	-	-
Crusting	1	2	2	3	-	-
Edema	0	0	1	1	-	-
Erosions	0	0	1	2	-	-
Erythema	0	1	2	3	-	-
Pruritus	0	0	1	1	-	-
Scaling	1	2	2	2	-	-
Stinging	0	0	0	1	-	-
Adverse Event: Myocardial Infarction (b) (6) resulting in death.						

The applicant considered this event to be unrelated to study medication, and this reviewer concurs that causality, or a safety signal of concern, is extremely unlikely given the accompanying medical history.

There were no deaths in any of the other clinical studies with Tolak (fluorouracil) Cream 4%.

7.1.2 Other Serious Adverse Events

49 serious, non-fatal adverse events were reported in the two phase 3 trials, 048 and 049. 23 occurred in subjects in the Tolak (fluorouracil) Cream 4% groups. None were considered to be related to study medication by the investigators. The overall rate for number of adverse events reported is similar between the Tolak (fluorouracil) 4% and Efudex 5% treatment groups, although the Efudex group received twice daily applications of study medication. However, the frequency of serious adverse events was higher in the Tolak (fluorouracil) 4% group (22 vs. 7; 11% vs. 3%). The serious adverse event data is summarized in the following table:

Clinical Review Table 16
Summary of Adverse Event Characteristics Study 048

	4% TRADENAME Cream (N=348)	Efudex® 5% Cream (N=342)	TRADENAME Vehicle (N=70)	Comparator Vehicle (N=65)
Number of Events Reported	203	211	29	28
Number of Subjects Who Reported One or More Events[a]	118 (34%)	122 (36%)	16 (23%)	13 (20%)
Serious[b]				
No	181 (89%)	204 (97%)	22 (76%)	20 (71%)
Yes	22 (11%)	7 (3%)	7 (24%)	8 (29%)
Severity[b]				
Mild	58 (29%)	69 (33%)	14 (48%)	20 (71%)
Moderate	91 (45%)	80 (38%)	8 (28%)	8 (29%)
Severe	54 (27%)	62 (29%)	7 (24%)	0 (0%)
Relationship to Study Medication[b]				
Unrelated	76 (37%)	45 (21%)	21 (72%)	25 (89%)
Unlikely	18 (9%)	19 (9%)	6 (21%)	3 (11%)
Possible	4 (2%)	14 (7%)	2 (7%)	0 (0%)
Probable	29 (14%)	37 (18%)	0 (0%)	0 (0%)
Related	76 (37%)	96 (45%)	0 (0%)	0 (0%)

[a] Proportion based on number of subjects.
[b] Proportion based on number of events.

Note: Subjects in the 4% TRADENAME Cream and TRADENAME Vehicle treatment groups applied study medication once daily. Subjects in the Efudex® 5% Cream and Comparator Vehicle treatment groups applied study medication twice daily.

In study 048, subjects were instructed to apply study medication once daily for 28 days. 348 subjects were randomized into the Tolak (fluorouracil) Cream 4% arm. Subjects applied an average of 26.3 applications of study medication over 26.5 days in the active Tolak (fluorouracil) group. 94% were compliant with the dosing regimen. Subjects were instructed to apply study medication once daily for 28 days.

203 adverse events were recorded in the Tolak (fluorouracil) Cream 4% cohort of which 22 (11%) were coded as serious adverse events.

These included basal cell carcinoma (from untreated areas on back and shoulder), dizziness from hypertension, appendicitis with abscess, vomiting with dehydration, bladder laser surgery, melanoma on the back, sepsis with leg, shoulder and eye cellulitis, hepatic encephalopathy, squamous cell carcinoma on the face diagnosed on the treatment completion date, enlarged prostate with urinary obstruction, heart attack, and colon cancer.

3 subjects in the Tolak (fluorouracil) 4% group had 4 basal cell carcinomas, one squamous cell carcinoma on the face, and one malignant melanoma lesion on the back diagnosed. Only one case of the basal cell lesions was on the treated areas (ear), and the squamous cell lesion was on the face. These cases presumably are related to lack of proper diagnostic assessment of the lesions at the time of study enrollment.

In the Efudex 5% group, 2 cases of basal cell carcinoma were reported as serious adverse events, as well as 5 actinic keratosis lesions on the temples and forehead of one subject which were treated with liquid nitrogen cryosurgery following study discontinuation due to application site erythema, stinging and itching.

There was one case of squamous cell carcinoma in the Tolak (fluorouracil) vehicle group (total subjects were 70). No serious adverse events in this group bore any relationship to signs or symptoms of allergy or anaphylaxis.

The applicant concluded that none of these serious adverse events were related to study medication. This reviewer concurs with that conclusion. No significant differences between the two active arms of study 048 were identified. No adverse events were reported that resembled any systemic allergy symptoms, or signs of anaphylaxis which is a theoretical concern due to the presence of (b) (4) peanut oil in the Tolak (fluorouracil) 4% formulation.

In study 049, subjects were instructed to apply study medication once daily for 28 days. 49 subjects were randomized into the Tolak (fluorouracil) Cream 4% arm. Subjects applied an average of 24.7 applications of study medication across 24.9 days.

21 of 49 subjects reported a total of 38 adverse events during the study. The one serious adverse event in the Tolak (fluorouracil) 4% group was the previously mentioned fatal myocardial infarction described above in section 7.1.1. The applicant and this reviewer again concur that this event is unlikely to be related to study medication. Four serious adverse events occurred in the vehicle group in three subjects, which included prostate cancer, syncope, squamous cell cancer on the ear, basal cell cancer on the back, and syncope.

One serious adverse event was reported in the phase 2 dose ranging trial 045. This subject with a history of hypertension, bypass surgery and diabetes developed acute renal failure and mile hyperkalemia necessitating hospital admission. The event resolved and the subject was discharged on the third hospital day.

The phase 1 contact sensitization study had 4 serious adverse events in three subjects. One was hysterectomy (underlying diagnosis not described), one had peripheral edema and increased INR, and one subject experienced a collapsed lung. The hysterectomy and collapsed lung were considered unrelated to study medication, while the peripheral edema and increase INR was classified as "possibly related" to study drug.

No serious adverse events were reported in the PK study 1206SA, the phototoxicity study 1106PT, and the photoallergy study 1206PA.

Reviewer comment: This reviewer concurs with the assessment that the relationship of the study drug with the serious adverse events is unlikely.

As stated in the OSE review of 5-fluorouracil post marketing events completed March, 25, 2008 as part of the post-marketing review for Carac Cream 0.5% (NDA 20-985), the significance of reported non-melanoma skin cancers in patients treated with 5-FU products

is unclear.

Although 5-FU is known to be carcinogenic in animal models, it is not known if the onset of a malignant process is progression of the actinic keratosis, is coincidental to the use of 5-FU, or actually represents an initiation or hastening of the malignant process in response to the use of 5-FU itself. The AERS database is not able to evaluate this possibility due to the latency between drug exposure and malignancy development.

The annual report for this product, dated December13, 2007 includes eight occurrences of non-melanoma skin cancer (NMSC) for study 048 in the reporting period subsequent to the end of the study (no cases of melanoma were reported.) The majority of these were in sites distant from those treated with Tolak (fluorouracil) Cream, e.g., shoulder, leg, abdomen or chest. The relationship at distant sites seems unlikely, and would presuppose a systemic effect on distant lesions from limited systemic absorption. No reports of NMSC were made for Study 049 in the annual report.

While it is theoretically possible that 5-FU products may contribute to a malignant process, it seems more likely to this reviewer that cases of non-melanoma skin cancer seen in the Tolak (fluorouracil) Cream 4% development studies are more likely the result of natural progression of actinically damaged skin, and not an effect of the Tolak (fluorouracil) Cream. No specific additions to labeling are suggested for this issue.

7.1.3 Dropouts and Other Significant Adverse Events

The number of subjects discontinuing completely from the phase 3 studies was similar across treatment arms in Studies 048 and 049 and ranged from 4% to 10%. The most common reason for subject dropout was subject decision to withdraw.

Clinical Review Table 17
Subjects Discontinuing from Study 048

	4% 5-FU	Efudex	Vehicle QD	Vehicle BID
Number of Subjects	353	349	70	69
Subjects who Discontinued Study	13 (4%)	20 (6%)	3 (4%)	7 (10%)
Adverse Event	2 (Sepsis, Burning/Stinging)	2 (Cracked Femur, Skin Reaction)	1 (Knee fracture)	-
Lost to Follow-Up	2	3	-	1
Noncompliance	-	2	-	-
Subject's Decision	9	12	2	6
Other	-	1 (Husb. in Hosp.)	-	-

Clinical Review Table 18
Subjects Discontinuing from Study 049

	4% 5-FU	Vehicle
Number of Subjects	50	50
Subjects who Discontinued Study	4 (8%)	4 (8%)
Adverse Event	-	2 (Dermatitis, Syncope)
Lost to Follow-Up	1	-
Noncompliance	1	-
Subject's Decision	1	-
Other	1 (Death)	2 (Out of Town [2])

Reviewer comment: Few subjects discontinued from the study completely. Few of this subset dropped out due to adverse events. A larger subject population terminated the treatment phase early due to adverse events (which were almost all local application site reactions), but completed the study by returning for the 4 week follow up visit. These subjects are described below, with tables from the statistical review by Dr. Fritsch.

Among subjects with dosing information available in Study 048, 4% 5-FU subjects applied treatment for a mean of 26.5 dosing days (range 2 to 35, N=346), Efudex subjects applied treatment for a mean of 25.8 dosing days (range 1 to 41, N=337), vehicle QD subjects applied treatment for a mean of 28.1 dosing days (range 11 to 33, N=70), and vehicle BID subjects applied treatment for a mean of 28.0 dosing days range (6 to 33, N=65).The following tables illustrated the subjects who completed treatment, or not, against subjects who completed the study or not:

Clinical Review Table 19
Number of Subjects Completing or Discontinuing Treatment and Completed Study Follow-up or Discontinued—Study 048

	4% 5-FU	Efudex	Vehicle QD	Vehicle BID
Number of Subjects	353	349	70	69
Subjects Completing Treatment	306 (87%)	270 (77%)	68 (97%)	63 (91%)
Subjects who Completed Study	304	269	66	62
Subjects who Discontinued Study	2	1	2	1
Subjects Discontinuing Treatment	47 (13%)	79 (23%)	2 (3%)	6 (9%)
Subjects who Completed Study	36	60	1	0
Subjects who Discontinued Study	11	19	1	6

Among subjects with dosing information available in Study 049, 4% 5-FU subjects applied treatment for a mean of 24.9 dosing days (range 7 to 44, N=48), and vehicle subjects applied treatment for a mean of 28.0 dosing days (range 6 to 36, N=50).

Clinical Review Table 20
Number of Subjects Completing or Discontinuing Treatment and Completed Study Follow-up or Discontinued—Study 049

	4% 5-FU	Vehicle
Number of Subjects	50	50
Subjects Completing Treatment	35 (70%)	48 (96%)
Subjects who Completed Study	34	45
Subjects who Discontinued Study	1	3
Subjects Discontinuing Treatment	15 (30%)	2 (4%)
Subjects who Completed Study	12	1
Subjects who Discontinued Study	3	1

The following tables for the phase 3 studies amplify the reasons for early treatment termination, which are almost all related to local application site reactions or subject withdrawal of consent.

Clinical Review Table 21
Reasons for Early Treatment Termination—Study 048

	4% 5-FU	Efudex	Vehicle QD	Vehicle BID
Number of Subjects	353	349	70	69
Subjects who Disc Trt	46	79	2	6
Adverse Event	35 (local AE [35])	49 (local AE [48])	2	-
Lost to Follow-Up	-	3	-	1
Noncompliance	-	1	-	-
Subject's Decision	11 (local AE [3])	18 (local AE [6])	-	5
Other	1 (local AE)	8 (local AE [5])	-	-

Clinical Review Table 22
Reasons for Early Treatment Termination—Study 049

	4% 5-FU	Vehicle
Number of Subjects	50	50
Subjects who Discontinued Trt	15	2
Adverse Event	11 (local AE [11])	2
Lost to Follow-Up	1	-
Noncompliance	1	-
Subject's Decision	1	-
Other	1	-

7.1.3.2 Adverse events associated with dropouts

The following section describes in further detail the adverse events which caused early treatment termination, and includes tables submitted by the applicant. The majority of these adverse events are local application site reactions which were not unexpected given the mechanism of action of 5-fluorouracil and the clinical experience with currently marketed 5-FU topical products.

Less than 15% of subjects in any treatment group discontinued study medication due to adverse events in the two phase 3 trials.

In Study 048, 88 of 825 (10.7%) subjects had adverse events that resulted in discontinuation of study medication. This included 35 of the 348 (10.1%) subjects randomized to Tolak (fluorouracil) Cream 4%. A slightly higher proportion of the Efudex subjects, 51 of 342 (14.9%) discontinued study medication. However, it is important to recognize that these subjects applied a stronger concentration (5%) twice daily instead on once daily applications. Over 90% of these adverse events in both groups were related to administration site reactions such as irritation, redness, pain, swelling, and itching.

Clinical Review Table 23
Adverse Events that Resulted in Discontinuation of Study Medication-Study 048

	4% TRADENAME Cream (N=348)	Efudex® 5% Cream (N=342)	TRADENAME Vehicle (N=70)	Comparator Vehicle (N=65)
Number of Subjects Who Discontinued Use of Study Mediation Due to Adverse Events	35 (10.1%)	51 (14.9%)	2 (2.9%)	0 (0.0%)
Adverse Event[a]				
General disorders and administration site conditions	32 (9.2%)	48 (14.0%)	0 (0.0%)	0 (0.0%)
Application site irritation	18 (5.2%)	21 (6.1%)	0 (0.0%)	0 (0.0%)
Application site reaction	9 (2.6%)	13 (3.8%)	0 (0.0%)	0 (0.0%)
Application site erythema	7 (2.0%)	11 (3.2%)	0 (0.0%)	0 (0.0%)
Application site pain	4 (1.1%)	7 (2.0%)	0 (0.0%)	0 (0.0%)
Application site pruritus	6 (1.7%)	6 (1.8%)	0 (0.0%)	0 (0.0%)
Application site erosion	2 (0.6%)	3 (0.9%)	0 (0.0%)	0 (0.0%)
Application site inflammation	1 (0.3%)	3 (0.9%)	0 (0.0%)	0 (0.0%)
Application site oedema	6 (1.7%)	2 (0.6%)	0 (0.0%)	0 (0.0%)
Application site dermatitis	0 (0.0%)	2 (0.6%)	0 (0.0%)	0 (0.0%)
Application site discomfort	2 (0.6%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Application site fissure	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Application site vesicles	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Application site bleeding	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Application site dryness	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a] Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 9.0) system organ classes and preferred terms. At each level of summarization (system organ class or preferred term) subjects are only counted once.

Note: Subjects in the 4% TRADENAME Cream and TRADENAME Vehicle treatment groups applied study medication once daily. Subjects in the Efudex® 5% Cream and Comparator Vehicle treatment groups applied study medication twice daily.

	4% TRADENAME Cream (N=348)	Efudex® 5% Cream (N=342)	TRADENAME Vehicle (N=70)	Comparator Vehicle (N=65)
Adverse Event[a]				
Infections and infestations	0 (0.0%)	5 (1.5%)	0 (0.0%)	0 (0.0%)
Application site infection	0 (0.0%)	3 (0.9%)	0 (0.0%)	0 (0.0%)
Impetigo	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Wound infection	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	2 (0.6%)	2 (0.6%)	0 (0.0%)	0 (0.0%)
Periorbital oedema	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Skin burning sensation	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Dermatitis	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood and lymphatic system disorders	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Lymphadenopathy	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Anaemia	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye disorders	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye irritation	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Paraneoplastic syndrome	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dizziness	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a] Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 9.0) system organ classes and preferred terms. At each level of summarization (system organ class or preferred term) subjects are only counted once.

Note: Subjects in the 4% TRADENAME Cream and TRADENAME Vehicle treatment groups applied study medication once daily. Subjects in the Efudex® 5% Cream and Comparator Vehicle treatment groups applied study medication twice daily.

Clinical Review Table 23 (continued)

	4% TRADENAME Cream (N=348)	Efudex® 5% Cream (N=342)	TRADENAME Vehicle (N=70)	Comparator Vehicle (N=65)
Adverse Event[a]				
Psychiatric disorders	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Insomnia	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertension	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Atrial fibrillation	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Injury, poisoning and procedural complications	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Head injury	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Lower limb fracture	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Wrist fracture	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)

[a] Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 9.0) system organ classes and preferred terms. At each level of summarization (system organ class or preferred term) subjects are only counted once.

Note: Subjects in the 4% TRADENAME Cream and TRADENAME Vehicle treatment groups applied study medication once daily. Subjects in the Efudex® 5% Cream and Comparator Vehicle treatment groups applied study medication twice daily.

In Study 049, a total of 13 subjects prematurely discontinued treatment due to adverse events, 11 in the TRADENMAE Cream group and 2 subjects in the vehicle group. All of these were related to application site reactions except one report of eye swelling.

Clinical Review Table 24
Adverse Events that Resulted in Discontinuation from Study 049

	4% TRADENAME Cream (N=49)	TRADENAME Vehicle (N=50)
Number of Subjects Who Discontinued Use of Study Mediation Due to Adverse Events	11 (22.4%)	3 (6.0%)
Adverse Event[a]		
General disorders and administration site conditions	11 (22.4%)	1 (2.0%)
Application site dermatitis	0 (0.0%)	1 (2.0%)
Application site irritation	3 (6.1%)	0 (0.0%)
Application site pain	3 (6.1%)	0 (0.0%)
Application site reaction	3 (6.1%)	0 (0.0%)
Application site erythema	2 (4.1%)	0 (0.0%)
Application site inflammation	2 (4.1%)	0 (0.0%)
Application site oedema	2 (4.1%)	0 (0.0%)
Application site dryness	1 (2.0%)	0 (0.0%)
Application site erosion	1 (2.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	1 (2.0%)
Basal cell carcinoma	0 (0.0%)	1 (2.0%)
Squamous cell carcinoma	0 (0.0%)	1 (2.0%)
Nervous system disorders	0 (0.0%)	1 (2.0%)
Syncope	0 (0.0%)	1 (2.0%)
Skin and subcutaneous tissue disorders	0 (0.0%)	1 (2.0%)
Dermatitis	0 (0.0%)	1 (2.0%)
Eye disorders	1 (2.0%)	0 (0.0%)
Eye swelling	1 (2.0%)	0 (0.0%)

[a] Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 9.0) system organ classes and preferred terms. At each level of summarization (system organ class or preferred term) subjects are only counted once.

In the phase 2 dose ranging study 045, 12 subjects discontinued prematurely due to adverse events, all of which had at least one adverse event related to study medication. Three subjects in the Tolak (fluorouracil) Cream 4% twice daily- 4 weeks treatment group, three subjects in the Tolak (fluorouracil) Cream 4% once daily- 4 week group, and

6 subjects in the Efudex Cream group discontinued due to adverse events. All of these were local reactions that included redness, crusting, pain and burning.

In the PK study 1206SA, nine subjects discontinued due to AE's, five in the Tolak (fluorouracil) Cream 4% group and four in the Efudex Cream 5% cohort. All of these were local administration site effects, though one subject in the Tolak (fluorouracil) group who previously reported burning, pain, swelling and scabbing developed impetigo on day 22 and was discontinued at that time.

No subject discontinued from the 1106PT phototoxicity study. Three subjects in the 1206PA photoallergy study withdrew due to AE's. All of these were local irritative effects.

Five subjects in the phase 1 1393 contact sensitization study withdrew due to AE's. The applicant provided the following table, with suspected relationship to the study medication, but all seem unlikely to be related except for the rash in subject 212:

Clinical Review Table 25
Withdrawals due to Adverse Events—Phase 1 Contact Sensitization Study R05-1393

Subject No.	Adverse Event[1]	Serious	Intensity	Relationship
055	Myalgia	No	Moderate	Possible
	Chills	No	Moderate	Remote
	Edema peripheral	Yes	Moderate	Possible
107	Vaginal discharge	No	Mild	Remote
129	Rash	No	Moderate	Probable
170	Collapse of lung	Yes	Severe	Unrelated
212	Headache	No	Moderate	Probable
	Back pain	No	Moderate	Probable
	Neck pain	No	Moderate	Probable
	Rash	No	Moderate	Probable

Source: PRACS R05-1393 CSR Table 12.2

7.1.5 Common Adverse Events

924 subjects across all studies comprised the safety population from the two phase 3 studies, 048 and 049. Of these, 296 (32%) subjects reported 517 adverse events. 171 subjects (19%) reported 290 adverse events that were considered by the investigator to be related to study medication.

The most common adverse events were application site reactions of irritation, pain, erythema, pruritus and edema. Given the considerable experience with 5-FU, these reactions were neither unusual nor unexpected.

Detailed analyses of common adverse events were not conducted for phase 1 and 2 trials because the application of medication was not typical of the intended clinical use. The common adverse reactions mirrored the phase 3 studies with most events related to application site reactions. Only the two phase 3 trials will be discussed in this section.

The following table presents a summary of adverse event data from the two clinical studies, 048, and 049.

Clinical Review Table 26
Summary of Adverse Events-Combined Phase 3 Studies 048 and 049

	4% TRADE-NAME Cream (N=397)	TRADE-NAME Vehicle Cream (N=120)	Efudex® 5% Cream (N=342)	Comparator Vehicle Cream (N=65)
Subjects with 1 or more events, n (%)	139 (35)	22 (18)	122 (36)	13 (20)
Number of Events	241	37	211	28
Number of SAEs, n (%)	23 (10)	11 (30)	7 (3)	8 (29)
Severity, n (%)				
Mild	67 (28)	15 (41)	69 (33)	20 (71)
Moderate	109 (45)	8 (22)	80 (38)	8 (29)
Severe	65 (27)	8 (22)	62 (29)	0
Relationship to Study Medication, n (%)				
Unrelated	80 (31)	27 (73)	45 (21)	25 (89)
Unlikely	21 (9)	7 (19)	19 (9)	3 (11)
Possible	6 (2)	2 (5)	14 (7)	0 (0)
Probable	43 (18)	1 (3)	37 (18)	0 (0)
Related	91 (38)	0 (0)	96 (45)	0 (0)
Most Common AEs, n (%)[1]				
Application Site				
Irritation	29 (7)	0 (0)	27 (8)	0 (0)
Pain	16 (4)	0 (0)	16 (5)	0 (0)
Reaction	16 (4)	1 (1)	15 (4)	0 (0)
Erythema	12 (3)	0 (0)	15 (4)	0 (0)
Pruritus	11 (3)	0 (0)	12 (4)	0 (0)
Edema	10 (3)	0 (0)	2 (1)	0 (0)

Source: Tables 14.3.1.2.2, 14.3.1.2.3

Discussion of the two studies follows below and data from the two studies 048 and 049 will be presented individually.

7.1.5.1 Eliciting adverse events data in the development program

All clinical adverse events, whether observed by the investigator or the subject were recorded whether or not they were drug related. Severity was recorded as mild, moderate, or severe. The relationship was assessed by the investigator as either unrelated, unlikely, possible, probable, or related.

In addition to collection of adverse event data, tolerability assessments were conducted that included erythema, scaling/dryness, crusting, pruritus, stinging/burning, edema, and erosions.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using the MedDRA Dictionary. Subjects were counted once per body system and once per preferred term.

7.1.5.3 Incidence of common adverse events

The most common adverse events were application site reactions of irritation, pain, erythema, pruritus and edema, which composed the overwhelming majority of common adverse events. These were also assessed separately in local tolerance scores described below in Section 7.1.5.5.

7.1.5.4 Common adverse event tables

Clinical Review Table 27
Adverse Events in > 1% of Subjects—Study 048 Safety Population

	4% 5-FU N=348	Efudex N=342	Vehicle QD N=70	Vehicle BID N=65
Subjects Reporting Events	118 (34%)	122 (36%)	16 (23%)	13 (20%)
Application site irritation	25 (7%)	27 (8%)	0 (0%)	0 (0%)
Application site reaction	12 (3%)	15 (4%)	0 (0%)	0 (0%)
Application site erythema	10 (3%)	15 (4%)	0 (0%)	0 (0%)
Application site pruritus	10 (3%)	15 (4%)	0 (0%)	0 (0%)
Application site pain	9 (3%)	16 (5%)	0 (0%)	0 (0%)
Application site edema	8 (2%)	2 (<1%)	0 (0%)	0 (0%)
Application site inflammation	3 (1%)	4 (1%)	0 (0%)	0 (0%)
Impetigo	2 (<1%)	7 (2%)	0 (0%)	0 (0%)
Nasopharyngitis	1 (<1%)	4 (1%)	1 (1%)	0 (0%)
Application site infection	0 (0%)	4 (1%)	0 (0%)	0 (0%)
Headache	1 (<1%)	6 (2%)	1 (1%)	0 (0%)
Diarrhea	5 (1%)	1 (<1%)	0 (0%)	1 (2%)
Nausea	4 (1%)	1 (<1%)	0 (0%)	1 (2%)
Vomiting	4 (1%)	0 (0%)	0 (0%)	0 (0%)
Eye irritation	4 (1%)	1 (<1%)	0 (0%)	0 (0%)
Back pain	4 (1%)	0 (0%)	1 (1%)	0 (0%)

Clinical Review Table 28
Adverse Events in > 1% of Subjects—Study 049 Safety Population

	4% 5-FU N=49	Vehicle N=50
Subjects Reporting Events	21 (43%)	6 (12%)
Application site pain	7 (14%)	0 (0%)
Application site reaction	4 (8%)	1 (2%)
Application site irritation	4 (8%)	0 (0%)
Application site erythema	2 (4%)	0 (0%)
Application site inflammation	2 (4%)	0 (0%)
Application site edema	2 (4%)	0 (0%)
Application site dermatitis	1 (2%)	1 (2%)
Application site pruritus	1 (2%)	0 (0%)
Application site dryness	1 (2%)	0 (0%)
Application site erosion	1 (2%)	0 (0%)
Application site paresthesia	1 (2%)	0 (0%)
Nasopharyngitis	1 (2%)	0 (0%)
Pharyngitis	1 (2%)	0 (0%)
Dementia Alzheimer's type	1 (2%)	0 (0%)
Headache	1 (2%)	0 (0%)
Angina pectoris	1 (2%)	0 (0%)
Myocardial infarction	1 (2%)	0 (0%)
Eye swelling	1 (2%)	0 (0%)
Joint swelling	1 (2%)	0 (0%)
Vein Discoloration	1 (2%)	0 (0%)

7.1.5.5 Identifying common and drug-related adverse events

Local, cutaneous adverse events were likely related to application of the study drug product. There is considerable experience with 5-FU products and the application site reactions are not unexpected.

Seven assessments of local tolerance (erythema, scaling/dryness, crusting, pruritus, stinging/burning, edema, and erosions) were assessed at every visit on a 4-point scale (0 – none, 1 – mild, 2 – moderate, 3 – severe). Each of these assessments increased in mean severity throughout the treatment period on the 5-FU arms, peaking at Week 4 (Visit 4). During the post-treatment period the mean severity returned to baseline levels. Subjects on vehicle treatment remained on average at baseline levels throughout the study. The mean values for the 4% 5-FU arm were slightly lower than the Efudex mean values.

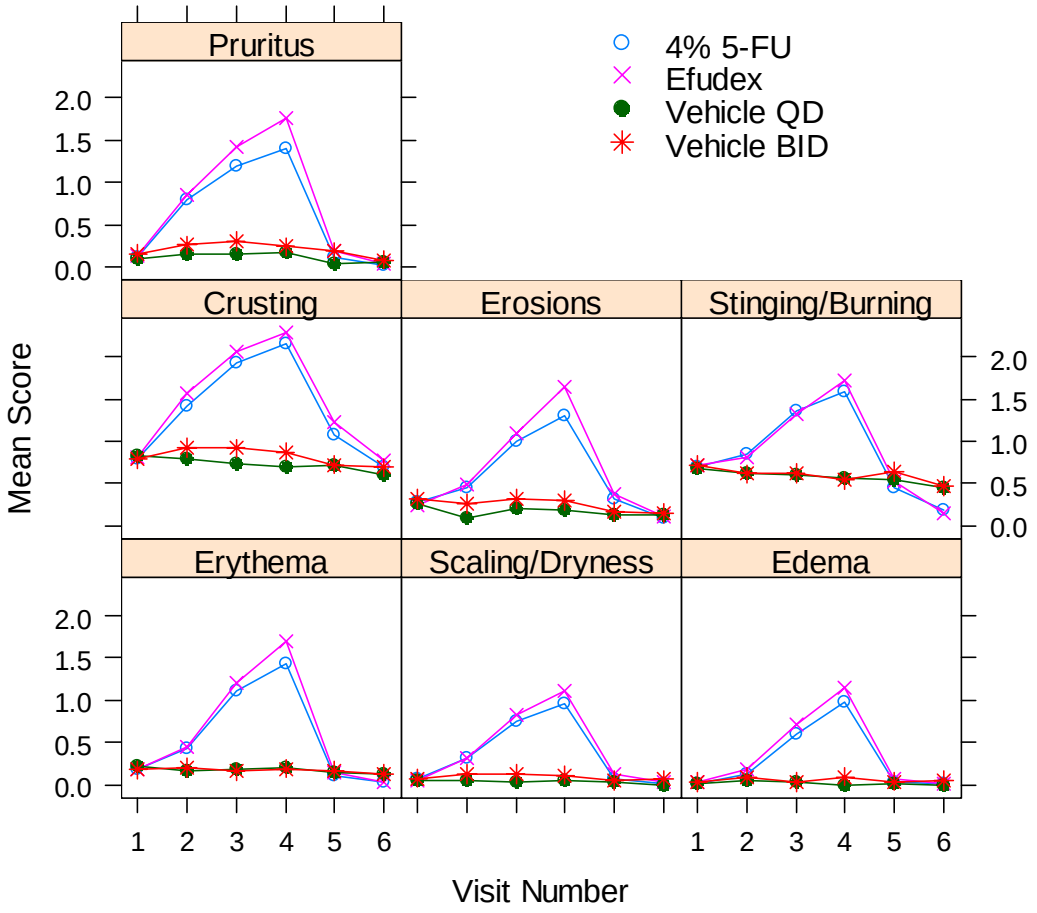
Reviewer comment: While the effects are similar, the Efudex reference product differs from Tolak (fluorouracil) Cream 4% in the concentration (higher in Efudex [5% vs. 4% in Tolak (fluorouracil) Cream] and in frequency of application [twice daily or Efudex vs. once daily for Tolak (fluorouracil) Cream].) This data should not be used to make either safety or efficacy claims of comparability or superiority compared to Efudex.

The mean local tolerance scores from the Agency analysis by Dr. Fritsch are provided below. Visit numbers for the local tolerance scores are:

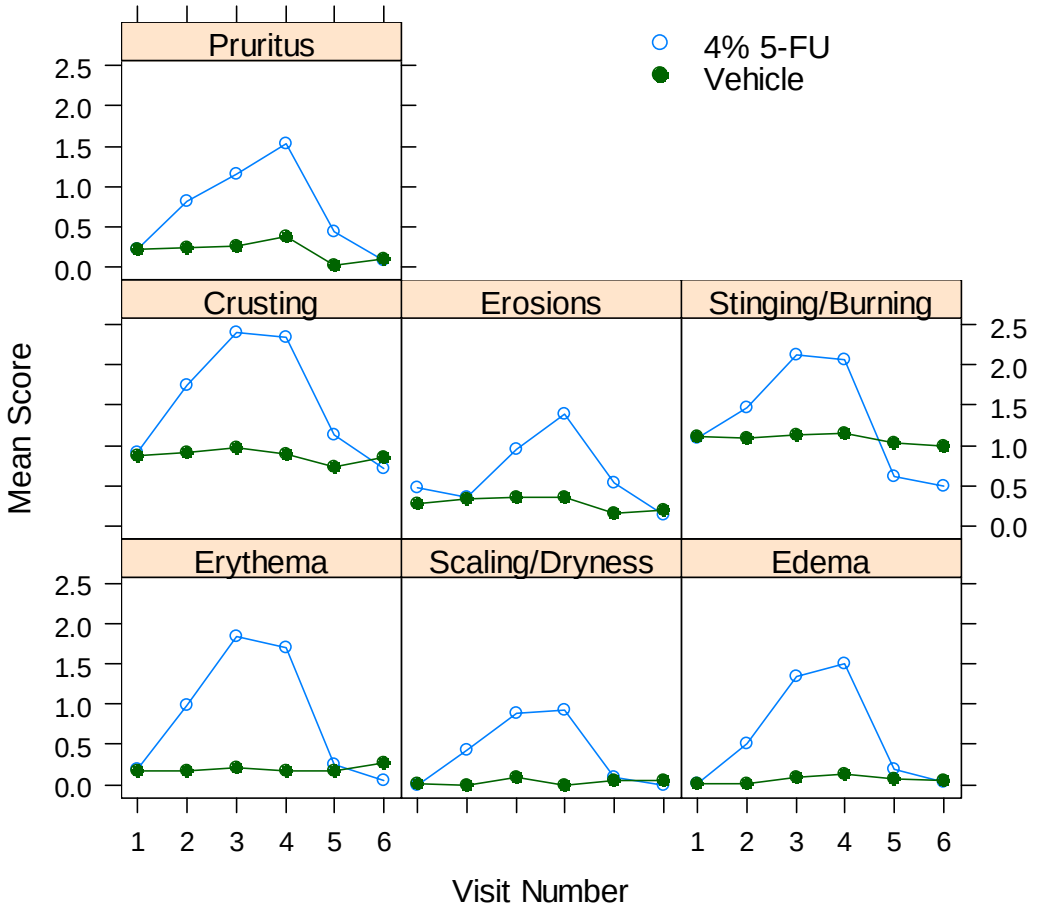
Visit 1	Baseline
Visit 2	Week 1
Visit 3	Week 2
Visit 4	Week 4
Visit 5	2 weeks off treatment
Visit 6	4 weeks off treatment (primary efficacy endpoint visit)

The peak incidence for application site effects occurs at visit 4, which correlates to the end of the four week treatment period. Almost all local effects returned to baseline by four weeks off treatment, which was the primary efficacy endpoint.

Clinical Review Table 29
Mean Local Tolerance Scores by Visit—Study 048



Clinical Review Table 30
Mean Local Tolerance Scores by Visit—Study 049



The vast majority of 5-FU subjects experienced local tolerance events, and many of them had severe events. The number of subjects who experienced any level of an assessment (mild, moderate, or severe) during the study along with the number of subjects experiencing severe events are presented in the following tables.

Clinical Review Table 31
Maximum Local Tolerance Assessment—Study 048

	4% 5-FU N=348		Vehicle QD N=70	
	All Grades*	**Severe**	**All Grades***	**Severe**
Erythema	345 (99%)	142 (41%)	55 (79%)	0 (0%)
Scaling/Dryness	328 (94%)	71 (20%)	49 (70%)	0 (0%)
Crusting	298 (86%)	69 (20%)	21 (30%)	0 (0%)
Pruritus	297 (85%)	58 (17%)	27 (39%)	0 (0%)
Stinging/Burning	300 (86%)	89 (26%)	22 (31%)	0 (0%)
Edema	234 (67%)	27 (8%)	5 (7%)	0 (0%)
Erosions	231 (66%)	34 (10%)	4 (6%)	0 (0%)
	Efudex N=342		**Vehicle BID N=65**	
	All Grades*	**Severe**	**All Grades***	**Severe**
Erythema	337 (99%)	169 (49%)	58 (89%)	2 (3%)
Scaling/Dryness	325 (95%)	84 (25%)	44 (68%)	1 (2%)
Crusting	315 (92%)	89 (26%)	19 (29%)	0 (0%)
Pruritus	305 (89%)	84 (25%)	30 (46%)	0 (0%)
Stinging/Burning	315 (92%)	116 (34%)	26 (40%)	0 (0%)
Edema	250 (73%)	34 (10%)	9 (14%)	0 (0%)
Erosions	259 (76%)	46 (13%)	10 (15%)	0 (0%)

Clinical Review Table 32
Maximum Local Tolerance Assessment—Study 049

	4% 5-FU N=49		Vehicle N=50	
	All Grades*	**Severe**	**All Grades***	**Severe**
Erythema	49 (100%)	32 (65%)	47 (94%)	0 (0%)
Scaling/Dryness	49 (100%)	23 (47%)	50 (100%)	0 (0%)
Crusting	48 (98%)	18 (37%)	25 (50%)	0 (0%)
Pruritus	40 (82%)	7 (14%)	19 (38%)	1 (2%)
Stinging/Burning	46 (94%)	12 (24%)	20 (40%)	0 (0%)
Edema	41 (84%)	3 (6%)	6 (12%)	0 (0%)
Erosions	40 (82%)	10 (20%)	10 (20%)	0 (0%)

7.1.6 Less Common Adverse Events

One subject was reported to have had an "anaphylactoid reaction" during study 048. This adverse event was listed by the applicant as "moderate in severity", but not serious and unlikely related to the study medication. The subject did not discontinue from the study.

The subject was a 66 year old American Indian/ Alaskan Native male at site number 18. Symptoms involved flushing of the face, dizziness, and a "general dysphoric feeling." He denied sore throat, cough, congestion, or other signs of an upper respiratory infection. The symptoms resolved within an hour upon moving to an air conditioned room. No wheeze was found on physical exam, and the application site redness was consistent with typical reactions to 5-fluourouracil medication.

Medication was interrupted for 72 hours at the direction of the investigator, but was restarted without any recurrence of these symptoms, or other signs of allergy. The subject had no history of asthma or other atopic diseases listed in the medical history form.

The investigator coded this as a possible "anaphylactoid reaction" (b) (4)

Reviewer comment: The history of the episode, as well as the rechallenge and completion of the study with no signs of allergic reaction, all argue against an allergy mediated reaction in this case. A vasovagal episode is more likely to explain the type and duration of symptoms.

(b) (4)

There are literature reports of anaphylaxis with systemic administration of 5-fluorouracil, most recently in 1999 in a 40 year old with ovarian cancer who completed treatment following successful desensitization (Reactions Weekly: Vol. 764(14): page 8, dated14 August 1999). This reviewer could find no case reports of anaphylaxis related to topical administration.

There are multiple literature reports of contact dermatitis associated with topical 5-fluorouracil use. The largest review reported fourteen patients, of whom eight reacted to 5-fluorouracil, and four to a vehicle component of Efudex Cream. There were also two patients who had positive reactions to propylene glycol and stearyl alcohol as well as to different dilutions of 5-fluorouracil (Meijer, B and de Waard-van der Spek, F, Contact Dermatitis 2007:57, 58-60).

No subject listed a reaction that could be related to contact allergy with Tolak Cream 4%, though the irritant dermatitis typically elicited by clinical use would be difficult to discern from contact allergy. Specifically, no local reactions were deemed to be related to the (b) (4) *peanut oil component of the vehicle. The issue of peanut oil is further discussed in Section 3.1 of this review.*

7.1.7 Laboratory Findings

Laboratory testing was conducted for Study 048, but not for Study 049.

As expected given the population studied, almost half of the subjects in each treatment group demonstrated abnormal serum cholesterol and/or triglycerides at baseline or day 28 measurements. Specimens were non-fasting.

Laboratory specimens were collected from 159 of 348 subjects in the Tolak (fluorouracil) Cream 4% cohort, 155 of 342 subjects in the Efudex 5% cream cohort, and 31 of 70 subjects in the Tolak (fluorouracil) vehicle cohort. Limited changes were seen in any group. The largest change for cholesterol or triglycerides was in the Efudex group.

Four subjects in the Tolak (fluorouracil) Cream 4% cohort had out-of-range laboratory results that were clinically significant at baseline or at the end of treatment.

An 86 year old woman had abnormal WBC, hematocrit and hemoglobin, and monocyte values at baseline. WBC and monocytes returned to normal range, but the anemia was unchanged at the end of the study. This subject had hypertension, anemia, and a paraneoplastic syndrome unrelated to study treatment.

A 68 year old man had increased creatinine (1.6 mg/dL) and uric acid (10.2 mg/dL) at baseline. The values remained high but were judged clinically insignificant at the conclusion of the study.

A 69 year old man had an elevated WBC count of 104,000 elevated LDH (431 U/L) and low platelets (111,000) at baseline. Further evaluations confirmed blasts in the peripheral smear and a diagnosis of chronic leukocytic leukemia.

An 86 year old man had a WBC of 17,000, low lymphocytes and high monocytes at the end of treatment. Baseline CBC evaluation was normal.

None of these laboratory deviations were thought to be related to study medication, and the applicant concluded that Tolak (fluorouracil) Cream 4% had no adverse impact on blood chemistry or hematology values.

Clinical laboratory tests were not performed in the second phase 3 Study 049. No routine laboratory examinations were performed in the five phase 1 or 2 protocols except for PK assessments.

Labeling for currently approved 5-fluorouracil topical products states (b) (4)

Reviewer comment: This reviewer recommends similar language to Tolak (fluorouracil) Cream 4% labeling regarding biopsy consideration, though this was not included in the proposed prescribing information submitted by the applicant in the current submission. The following recommended language from the OSE review should be included:

> *Lesions that do not respond to an adequate course of therapy with Tolak (fluorouracil) Cream should be considered for excision and histologic examination to rule out more advanced skin cancer (basal cell carcinoma, squamous cell carcinoma, and melanoma). Patients with residual actinic keratoses following treatment with Tolak (fluorouracil) Cream should be considered for another treatment modality.*

The OSE reviewer recommends consideration of (b) (4) *It would seem reasonable to include this event in the Tolak (fluorouracil) Cream label as well though no adverse events related to low blood counts were seen in the phase 3 trial (048) that included laboratory analysis.*

The statement (b) (4)

The 69 year old subject in study 048 with CLL raises concern, but the issue of a safety signal between the development of chronic lymphocytic leukemia and the application of topical 5-fluorouracil drug products was reviewed by OSE in August, 2002, and a safety signal was not identified.

The most recent OSE review of post-marketing reports related to 5-fluorouracil topical products (as part of the review of Carac Cream 0.5% post-marketing studies) reviewed malignancy cases from 1977 to February, 2008:

> "Eight of the 15 malignancy cases described leukemia related malignancies. In this subgroup there were six male and two female patients, and the types of leukemia reported included chronic lymphocytic leukemia (4), acute myelogenous leukemia (1), acute non-lymphoblastic leukemia (1), acute lymphoblastic leukemia (1) and acute leukemia (1). The age of the leukemia patients ranged from 36 years to 82 years old, with a median age of 70.5 years (n = 8). The onset of diagnosis of leukemia in these patients varied and ranged from one week to 6 years after exposure, with a median time to onset of 6 months (n = 7).23 The duration of topical 5FU therapy was also varied and ranged from 7 days to 5 years, with a median duration of 16.5 days (n = 6)."

The OSE review did not recommend any changes to labeling regarding leukemia.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital sign data was not collected in Study 048 or 049 for this topical product.

7.1.9 Electrocardiograms (ECGs)

No electrocardiogram data was collected during any phase of drug development.

Reviewer comment: EKG assessments were not needed for this topical product.

7.1.11 Human Carcinogenicity

Reviewer comment: While it is theoretically possible that 5-FU products may contribute to a malignant process, it seems more likely to this reviewer that cases of non-melanoma skin cancer seen in the Tolak (fluorouracil) Cream 4% development studies are more likely the result of natural progression of actinically damaged skin, and not an effect of the Tolak (fluorouracil) Cream. No specific additions to labeling are suggested for this issue.

The review of consultations from the Office of Surveillance and Epidemiology regarding this issue is contained in Section 7.1.2.

7.1.12 Special Safety Studies

The applicant conducted several dermal safety studies to support labeling.

Study HD-FU1106PT assessed the potential of Tolak (fluorouracil) Cream 4% to induce skin irritation after UV radiation compared with non-irradiated controls following application of patches containing Tolak (fluorouracil) Cream 4%, Tolak (fluorouracil) vehicle, or a blank patch.

33 Subject were enrolled in the study, meeting the End of Phase 2 guidance that stated 30 subjects would be required.

No subjects were determined to have a phototoxicity reaction in this study.

Erythema scores at 24 hours are listed in the following table. The one hour and the 24 hour time points showed the highest erythema scores. The amount of erythema diminished at 48-72 hours.

Clinical Review Table 33
Erythema Scores at 24 Hours in Phototoxicity Study 1106PT

n (%) of Subjects with Erythema Grade[1] (N=33)	Non-Irradiated Sites: Test Article			Irradiated Sites: Test Article		
	4%TRADE-NAME	Vehicle	Blank	4%TRADE-NAME	Vehicle	Blank
0	30 (90)	31 (94)	30 (90)	8 (24)	9 (28)	9 (27)
0.5	1 (3)	1 (3)	2 (6)	15 (45)	16 (48)	17 (52)
1	2 (6)	1 (3)	1 (3)	10 (30)	8 (24)	7 (21)
2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Study HD-FU1106PT CSR, Table 14.2.2

1. Scale: 0=no visible reaction; 0.5=slight, confluent or patchy erythema; 1=mild erythema (pink); 2=moderate erythema (definite redness); and 3=strong erythema (very intense redness)

Study HD-FU1206PA assessed the potential of Tolak (fluorouracil) Cream 4% to induce skin irritation after UV irradiation compared with non-irradiated controls following application of patches containing either Tolak (fluorouracil) Cream 4%, Tolak (fluorouracil) vehicle, or a blank patch during an induction phase and then a challenge phase.

60 subjects were enrolled in this trial, satisfying the End of Phase 2 meeting guidance that stated 50 subjects would be required.

A smaller percentage of subjects showed irritation at the active patch site compared with either the vehicle or the blank patch site. The applicant concluded that there was no evidence of photo-allergenicity after exposure to either Tolak (fluorouracil) Cream 4% or its vehicle.

Clinical Review Table 34
Erythema Scores at 1 Hour Post-Irradiation in Photoallergy Study 1206PA Challenge Phase

n (%) of Subjects with Erythema Grade[1] (N=50)	Non-Irradiated Sites: Test Article			Irradiated Sites: Test Article		
	4%TRADE-NAME	Vehicle	Blank	4%TRADE-NAME	Vehicle	Blank
0	50 (100)	50 (100)	45 (90)	35 (70)	33 (66)	30 (60)
0.5	0 (0)	0 (0)	0 (0)	3 (6)	3 (6)	5 (10)
1	0 (0)	0 (0)	5 (10)	12 (24)	14 (28)	15 (30)
2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Study HD-FU1206PA CSR, Tables 11.4.1-1, 11.4.1-2, 11.4.1-3, 11.4.1-4, 11.4.1-5, and 11.4.1-6

1. Scale: 0=no visible reaction; 0.5=slight, confluent or patchy erythema; 1=mild erythema (pink); 2=moderate erythema (definite redness); and 3=strong erythema (very intense redness)

Study PRACS R05-1393 examined the contact sensitization (allergic contact dermatitis) potential and found no evidence of sensitization in any subject after exposure to Tolak (fluorouracil) Cream 4%. Five subjects had initial skin reactions at the 96 hour evaluation of the challenge phase, but upon re-challenge, no visible erythema or edema was present.

This contact sensitization study enrolled 231 subjects, satisfying the End of Phase 2 meeting guidance that stated 200 subjects would be required.

Cumulative irritancy evaluations were waived, since the applicant agreed at the End of Phase 2 meeting that Tolak (fluorouracil) Cream 4% would be labeled as an irritant.

Adverse events that led to study discontinuation are discussed in section 7.1.3.2. These included three subjects in the photoallergy study and five in the contact sensitization study.

Reviewer comment: The following language in the label is suggested for photosensitivity in section 5.2 of the Warnings and Precautions section of the label:

> **5.2 Photosensitivity:**
> Exposure to ultraviolet rays including sunlight should be minimized during and immediately following treatment with Tolak (fluorouracil) because the intensity of the reaction may be increased.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no known adverse effects following withdrawal of topical 5-FU products or Tolak (fluorouracil) Cream 4% in particular. Facial irritation improved and generally

returned to baseline by approximately 4 weeks post treatment. No reports of withdrawal or rebound phenomena were received in the clinical trials.

7.1.14 Human Reproduction and Pregnancy Data

No pregnancies were reported in any study in this application.

In an OSE review of US post-marketing reports completed for the evaluation of Carac Cream 0.5%, one case of pregnancy exposure was reported:

> One case described pregnancy exposure in the first trimester. After approximately 7 weeks gestation the fetal heart rate was discovered absent and a subsequent dilation and curettage was performed. Based on the report, the mother may have used Carac 20 days during her pregnancy. The mother had a history of one live birth, and one spontaneous abortion prior to 20 weeks gestation.

Labeling similar to current products is recommended, and pregnancy category X is consistent with other topical fluorouracil products.

4 CONTRAINDICATIONS

4.1 **Pregnancy** (b) (4)
TRADENAME may cause fetal harm when administered during pregnancy and is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 **Teratogenic Effects: Pregnancy Category X.**

(b) (4)

(b) (4)

Animal reproduction studies have not been conducted with TRADENAME. Fluorouracil administered parentally (b) teratogenic in mice, rats, and hamsters when given at (b) (4) doses equivalent to the usual human intravenous dose. However, the amount of fluorouracil absorbed systemically after topical administration to actinic keratoses is minimal [see *Clinical Pharmacology* (12.3)]. 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 embryolethality). 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. Based on the recommended human dose and instructions for use, it is not possible to calculate human dose equivalents for animal exposures in these studies.

Please refer to the Pharmacology/Toxicology Review for labeling recommendations for Section 13, Nonclinical Toxicology.

7.1.16 Overdose Experience

There are no known overdose reports in patients with topical 5-FU use.

Van Ruth et al. published a paper (Pharm World Sci (2006) 28:159-162) describing total body application of 5-FU 5% cream in two patients with extensive NMSC. Application was made to both normal and diseased areas of skin. No detectable serum levels were measured in weekly blood samples.

The first subject was treated twice weekly using 20 g per application, and the second treated twice daily using 13 g per application and a total dose of 400 g.

The first subject developed *Staphylococcal aureus* sepsis requiring intravenous antibiotics, and the second developed bacterial super-infection treated with oral antibiotics. Both subjects recovered with no epithelial tumors at six months follow-up visits.

While both subjects had infectious complications of their treatment, assessment of serum levels never showed detectable levels.

7.1.17 Postmarketing Experience

There is no post-marketing experience to date for this product. There is extensive experience with 5-FU products since the 1960's. Currently approved and marketed topical formulations are listed in section 2.3 of this clinical review.

Consultations with the Office of Surveillance and Epidemiology were not obtained for this specific product application. However, a request for consultation was sent by DDDP to the Division of Drug Risk Evaluation (DDRE and currently reorganized as the Division of Epidemiology and the Division of Adverse Event Analysis I) to review the post marketing study report of Carac Cream, 0.5% (fluorouracil cream, 0.5%) and to comment on "the incidence of the carcinoma of the skin reported, ocular irritation, adequacy of the study, implications for labeling, etc." Information and labeling recommendations are included in this review in Section 8.8 of this review as it applies to 5-fluorouracil topical products for the treatment of actinic keratosis.

In addition, DDDP requested a summary of postmarketing adverse event (AE) reports for Carac Cream, 0.5% and for the class of topical fluorouracil drug products. Their analysis provided an overall review of the post-marketing adverse event reports submitted for all topical 5-FU drug products, drug use information, a review of the reports submitted specifically for Carac®, and a review of Carac® associated medication errors. The conclusions of this review are listed in Section 8.8 of this clinical review.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.3 Adequacy of Overall Clinical Experience

The overall exposure in terms of numbers of subjects and duration of exposure is acceptable to assess the safety of the product for its intended use. The designs of the studies were adequate to address safety concerns. Topical safety was adequately assessed in the development program.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the safety data was adequate. However, the safety update was not received until late March, 2008, and it failed to include some adverse events reports that were submitted to the IND annual report of December 13, 2007.

7.2.9 Additional Submissions, Including Safety Update

A safety update was submitted on March 19, 2008. A summary report for Study HD-FUPLTS-050, an Open Label, Multi-center, Uncontrolled, Single-group Assignment, Long-term Safety Study of Tolak (fluorouracil) Cream 4% in Subjects with Actinic Keratosis, was presented in the safety update. The full study report has not yet been submitted to date.

This study was conducted to evaluate the long term safety of Tolak (fluorouracil) and to evaluate the recurrence rate of actinic keratoses in subjects previously treated with Tolak (fluorouracil) in studies 048 and 049. Subjects who were completely cleared (lesion count of 0) at the end of either 048 or 049 were evaluated at six and 12 months following the completion of the original pivotal study.

Subjects who were not completely cleared at the end of either study could be re-treated with Tolak (fluorouracil) for 4 weeks once daily and assessed again at 4 weeks and 8 weeks and evaluated for recurrence and safety at 6 months and 12 months following completion of the 048 or 049 studies.

310 subjects were enrolled, and 307 completed the study. One subject discontinued following hospitalization and surgery for an ankle fracture after a fall. One moved out of state. The remaining discontinued subject enrolled late and needed to be retreated.

The mean age of the 310 subjects in this safety population was 68.7 years, compared with 677 years in the two phase 3 trials. 251 (81%) were male, and 306 (99%) were white, which are the same as in the phase 3 trials. Of the 310 subjects enrolled, 104 933.5%) were retreated with study medication.

There were no deaths in this long term study.

19 serious adverse events were reported, of which 18 were judged by the applicant to be unrelated to study medication. One event was judged as “unlikely” to be related. This was a 77 year old male who completed 28 applications of study medications and was noted the next week to have basal cell carcinoma at four different sites (left hand, left ear, right chest, and right forehead). The lesions on his left ear and right chest were already adequately treated (with the study medication), while the lesions on his left hand and right forehead were treated with curettage and electrodessication five months later. No further treatment was required.

The other serious adverse events, judged by the applicant as unrelated, included squamous cell carcinomas and basal cell carcinomas, but most of these lesions occurred on body sites distinct from the treated areas. Other SAE's included aortic aneurysm repair, knee replacement, and a scalp keratoacanthoma.

Two subjects discontinued the treatment phase prematurely due to application site irritation (at days 18 and 23). Both subjects completed the study with these abbreviated courses of study medication. Another subject ended the treatment phase early (at 7 days) due to mild dermatitis as the application site (as opposed to treatment irritation), but completed the study.

Clinical Review Table 35
Serious Adverse Events in Long Term Safety Study 050

ID	Number of events	Adverse Event (AE)	Diagnosis	Procedure
2-51	1	Fall at home	Right ankle fracture	hospitalized/surgery
4-166	1	Lesion on the scalp	keratoacanthoma	surgery
9-40	1	Chest pain/ tightness		hospitalized
10-327	1	Lesion/ l dorsal hand	Squamous cell carcinoma	surgery
10-330	1	Lesion/ r posterior ear	Nodular basal cell carcinoma	surgery
	1	Lesion/re-current r forearm	Squamous cell carcinoma	
11-24	1	osteoarthritis	Left knee replacement	hospitalized/surgery
11-27	1	l dorsal hand keratotic plaque	Squamous cell carcinoma	surgery
15-337	1	Lesion/l calf	Basal cell carcinoma	surgery
	4	Lesion/r chest, l.ear, l hand, r forehead	Squamous cell carcinoma	surgery
16-148	1	Enlarged prostate		hospitalized/surgery
19-381	1	Physical weakness	Small hiatal hernia, ulcer, duodenitis	hospitalized
21-139	1	Lesion/r anterior shoulder	Basal cell carcinoma	surgery
102-394	1	Lesion/r lateral back	Basil cell carcinoma	surgery
	1	Lesion/r jaw	Squamous cell carcinoma	surgery
102-391	1	Aortic aneurysm repair		hospitalized/surgery
	2	Blocked arteries		
103-4	2	Lesions on the hand	Squamous cell carcinoma	surgery
103-8	1	Lesion/r forehead	Solar lentigo/maligna	surgery

The most common adverse events, as in the phase 3 studies, were application site erythema, irritation, pruritus, discharge and scabbing. Most (91%) of these local application site reactions were considered mild to moderate in severity.

A summary of adverse events is included in the following table:

Clinical Review Table 36
Summary of Adverse Events: Long Term Safety Study 050

	Long-term Safety Study (N = 310)
Subjects with 1 or more events[a], n (%)	57 (18.4)
Number of Events	102
Number of SAEs[b], n (%)	19 (18.6)
Severity[b], n (%)	
Mild	59 (57.8)
Moderate	34 (33.3)
Severe	9 (8.8)
Relationship to Study Medication[b], n (%)	
Unrelated	56 (54.9)
Unlikely	6 (5.9)
Possible	0
Probable	4 (3.9)
Related	36 (35.3)
Most Common AEs[a], n (%)[1]	
General disorders and administration site conditions	23 (7.4)
Application site erythema	9 (2.9)
Application site irritation	7 (2.3)
Application site pruritus	5 (1.6)
Application site discharge	4 (1.3)
Application site scab	4 (1.3)
Neoplasms	13 (4.2)
Squamous cell carcinoma of skin	7 (2.3)
Basal cell carcinoma	4 (1.3)

[a] Proportion based on number of subjects.
[b] Proportion based on number of events.
[1] Counts reflect number of subjects reporting one or more AE classified to MedDRA. At each level of summarization (system organ class or preferred term) subjects are counted only once (under the highest likely attribution)

Reviewer comment: The adverse events observed in this long term study were similar to those seen in the two phase 3 trials reviewed earlier. Most of the adverse events were related to application site reactions, and labeling for existing 5-fluourouracil products reflects this, and draft labeling submitted for this product is similar. The discontinuation rate in this population (3%) is less than the 15% rate that discontinued from the phase 3 studies due to adverse events.

Most of the skin neoplasms seen in long term follow-up were on sites other than scalp, face and ears and are thus unrelated to the topical application of this product.

In typical clinical practice, most subjects with persistent or recurrent actinic keratoses would be treated with alternative therapies rather than repeating another four week course of 5-fluourouracil. The irritating nature of the product will limit its repeated use in actual practice. However, some of these subjects completed two four week courses of Tolak (fluorouracil) cream with few discontinuations due to adverse events, and no additional

safety concerns.

For comparison to the all the studies described above, the applicant provided the following summary table of adverse events for all the clinical studies for Tolak (fluorouracil) Cream 4%:

Table 8 Summary of Adverse Events: Combined Clinical Studies

	Primary Clinical Studies (48 & 49) 5-FU Cream / Efudex (N=397) / (N = 342)	Dose Ranging Study HDFUDR-045 5-FU Cream / Efudex (N = 81) / (N = 20)	Pharmacokinetic Study HDFU1206SA 5-FU Cream / Efudex (N = 21) / (N = 22)	Photo-toxicity Study HDFU1106PT (N=33)	Photo-allergenicity Study HDFU1206PA (N = 60)	Contact Sensitization Study PRACS R05-1393 (N = 231)	Long-term Safety Study (N = 310)
Subjects with 1 or more events[a], n (%)	139 (35) / 122 (36)	80 (99) / 20 (100)	21 (100) / 22 (100)	3 (9)	24 (40)	74 (32)	57 (18.4)
Number of Events	241 / 211	231 / 71	94 / 97	5	39	132	102
Number of SAEs[b], n (%)	23 (10) / 7 (3)	1 (<1) / 0	0 / 0	0	0	4 (3)	19 (18.6)
Severity[b], n (%)							
Mild	67 (28) / 69 (33)	109 (47) / 26 (37)	67 (71) / 67 (69)	5 (100)	27 (69)	78 (59)	59 (57.8)
Moderate	109 (45) / 80 (38)	97 (42) / 33 (46)	25 (27) / 23 (24)	0	11 (28)	53 (40)	34 (33.3)
Severe	65 (27) / 62 (29)	25 (11) / 12 (17)	2 (2) / 7 (7)	0	1 (3)	1 (<1)	9 (8.8)
Relationship to Study Medication[b], n (%)							
Unrelated	80 (33) / 45 (21)	3 (1) / 1 (1)	1 (1) / 6 (6)	5 (100)	32 (82)	79 (60)	56 (54.9)
Unlikely	21 (9) / 19 (9)	11 (5) / 2 (3)	3 (3) / 2 (2)	NA	NA	22 (17)	6 (5.9)
Possible	6 (2) / 14 (7)	3 (1) / 1 (1)	10 (11) / 10 (10)	0 (0)	3 (8)	16 (12)	0
Probable	43 (18) / 37 (18)	34 (15) / 6 (8)	3 (3) / 5 (5)	0 (0)	2 (5)	15 (11)	4 (3.9)
Related	91 (38) / 96 (45)	180 (78) / 61 (86)	77 (82) / 74 (76)	0 (0)	2 (5)	0	36 (35.3)
Most Common AE[a]s,n (%)[1]							
Application Site							23 (7.4)
Irritation	29 (7) / 27 (8)	31 (38) / 12 (60)					7 (2.3)
Pain	16 (4) / 16 (5)	20 (25) / 4 (20)	9 (43) / 8 (36)				1 (0.3)
Reaction	16 (4) / 15 (4)	27 (33) / 9 (45)					1 (0.3)
Erythema	12 (3) / 15 (4)	80 (99) / 20 (100)	14 (67) / 16 (73)				9 (2.9)
Pruritus	11 (3) / 12 (4)	21 (26) / 8 (40)	12 (57) / 5 (23)			5 (2)	5 (1.6)
Edema	10 (3) / 2 (1)						
Inflammation	5 (1) / 4 (1)						
Desquamation / Skin exfoliation		11 (14) / 5 (25)	4 (19) / 2 (9)				
Bleeding		6 (7) / 2 (10)					
Discharge							4 (1.3)
Scab			6 (29) / 2 (9)				4 (1.3)

[a] Based on number of subjects. [b] Based on number of events.
Source: ISS Tables 10, 11, 12, 13 and Tables 14.3.1.2.1, 14.3.1.2.2, and 14.3.1.3.4

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

5-fluorouracil is a well established molecular entity and its adverse event profile is reasonably well understood over decades of clinical use. The common side effects of skin irritation, dryness, redness, and peeling are predictable and labeling is adequate to address these safety concerns. There were no significant non-skin related adverse events demonstrated in the development program.

7.4 General Methodology

7.4.3 Causality Determination

It is likely that the local dermatologic adverse events of skin dryness, burning, redness, and peeling were causally related to the studied product, Tolak (fluorouracil) (5-fluorouracil) Cream 4%. The other reported adverse events which occurred at a frequency ≥ 1% are unlikely to be causally related to the 5-FU product.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The applicant has submitted two phase 3 studies with once daily applications for four weeks. The reference product, Efudex Cream 5%, is labeled for twice daily applications for four weeks.

Study 045 examined the use of Tolak (fluorouracil) Cream 4% in 20 subject arms with treatment for once daily, twice daily applications, and treatment durations for two and four weeks.

8.2 Drug-Drug Interactions

Drug-drug interactions with other medications were not assessed. While sunscreens and emollient cream could be applied, no other topical medications were allowed to be used in the treatment area. Treatment with retinoids, immunosuppressants, immunomodulators, glycolic acid products, alpha-hydroxy acid products, and chemical peel products were specifically excluded. Labeling for currently approved products does not list any drug-drug interactions.

8.3 Special Populations

The applicant's efforts to evaluate the effects of age, gender or skin type/race and ethnicity on efficacy were adequate given the prevalence of actinic keratosis. The population studied averaged 68 years of age and correlates with the population affected with actinic keratoses. There was no evidence of clinically significant effect of any of these parameters on efficacy.

8.4 Pediatrics

The applicant has submitted a full pediatric waiver request based on information that actinic keratoses grow slowly and typically require years to develop in reaction to photo-damaged skin. They state "the pediatric population would show no definable signs or

symptoms of actinic keratoses applicable for use of the product until reaching an advanced age. Hill requests a full waiver since this drug product does not represent a meaningful benefit over existing treatments for pediatric patients and is not likely to be used in pediatric patients."

While the antecedent sun exposure important in the development of actinic keratoses occurs in childhood, the development of actual actinic lesions requiring treatment is exceedingly rare. A full waiver is recommended by this reviewer as the product is not likely to be used in the pediatric age group. The following labeling suggested by the applicant is acceptable:

> **8.4 Pediatric Use**
>
> Actinic keratosis is not usually observed in the pediatric population except in the case of rare genetic diseases. Tolak (fluorouracil) is not intended for use in (b) (4). Safety and effectiveness in children have not been established.

8.7 Postmarketing Risk Management Plan

Study HD-FUPLTS-050, an Open Label, Multi-center, Uncontrolled, Single-group Assignment, Long-term Safety Study of Tolak (fluorouracil) Cream 4% in Subjects with Actinic Keratosis, was conducted to evaluate the long term safety of Tolak (fluorouracil) and to evaluate the recurrence rate of actinic keratoses in subjects previously treated with Tolak (fluorouracil) in studies 048 and 049. Subjects who were completely cleared (lesion count of 0) at the end of either 048 or 049 were evaluated at six and 12 months following the completion of the original pivotal study.

Subjects who were not completely cleared at the end of either study could be re-treated with Tolak (fluorouracil) for 4 weeks once daily and assessed again at 4 weeks and 8 weeks and evaluated for recurrence and safety at 6 months and 12 months following completion of the 048 or 049 studies.

The safety update, submitted March 19, 2008, includes summary information for this long term study. The full study report has not yet been submitted.

It is recommended that a post-marketing commitment be included in the action for this application to require the submission of the final study report for the long term safety study 050 by six months from the action date for this application.

8.8 Other Relevant Materials

Consultations with the Office of Surveillance and Epidemiology were not obtained for this specific product application. However, a request for consultation was sent by DDDP to the Division of Drug Risk Evaluation (DDRE and currently reorganized as the Division of Epidemiology and the Division of Adverse Event Analysis I) to review the post marketing study report of Carac Cream, 0.5% (fluorouracil cream, 0.5%) and to comment on "the incidence of the carcinoma of the skin reported, ocular irritation, adequacy of the study, implications for labeling, etc." The following information is included in this review as it applies to 5-fluorouracil topical products for the treatment of actinic keratosis.

(b) (4)

(b) (4)

These suggestions are recommended for inclusion in the product labeling for Tolak (fluorouracil) Cream 4%.

In addition, DDDP requested a summary of postmarketing adverse event (AE) reports for Carac Cream, 0.5% and for the class of topical fluorouracil drug products. Their analysis provided an overall review of the post-marketing adverse event reports submitted for all topical 5FU drug products, drug use information, a review of the reports submitted specifically for Carac®, and a review of Carac® associated medication errors.

5-fluorouracil products were previously reviewed by OSE on two occasions:

(b) (4)

OSE conducted a query of the AERS database for all adverse event reports submitted for the topical 5-FU products. We identified the most commonly reported adverse events, as well as identified adverse events identified by data-mining as potential safety signals. Also reviewed were the 22 crude count post-marketing reports submitted specifically for (b) (4)

The most significant concern in these post-marketing reports was one case of death occurring after pneumonia subsequent to pancytopenia, described in a patient who used the higher concentration topical fluorouracil product. Details for dosing or indication were not provided, only that patient used Efudex in "high doses" for "months" for an unknown indication. Systemic serum levels were not provided.

Pancytopenia is a labeled adverse event of injectable and oral fluorouracil products, but not for the higher concentration topical fluorouracil products.

Reviewer comment: The OSE reviewer recommends consideration of adding pancytopenia to the labels (b) (4) *. It would seem reasonable to include this event to the Tolak (fluorouracil) Cream label as well though no adverse events related to low blood counts were seen in the phase 3 trial (048) that included laboratory analysis.*

Information regarding eye irritation and conjunctivitis should also be included as recommended by both OSE reviews.

9. OVERALL ASSESSMENT

9.1 Conclusions

This reviewer recommends that Tolak (fluorouracil) Cream 4% be approved for the topical treatment of actinic keratosis of the face, scalp, and ears. The applicant has presented adequate evidence from two well-controlled studies that the proposed 4% concentration of this product once daily is superior to vehicle in the treatment of actinic keratosis for four weeks.

The most common adverse events are local irritative effects such as redness, pain, itching and peeling. There were no deaths and no serious adverse events other than local application site reactions which were considered to be related to Tolak (fluorouracil) Cream 4%.

9.2 Recommendation on Regulatory Action

Approval is recommended for NDA 22-259, Tolak (fluorouracil) Cream 4% for the indication of actinic keratosis of the scalp, face, and ears.

The applicant has submitted under section 505(b)(2) and has referenced Efudex Cream 5% as the comparator product. There are currently no approved 5-fluorouracil products at the 4% concentration.

The first phase 3 study failed to show non-inferiority to Efudex Cream, though superiority to vehicle was demonstrated. A second phase 3 study compared Tolak (fluorouracil)

Cream 4% to vehicle and again confirmed superiority of the drug product to the vehicle.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Risk management will be addressed through labeling, which is similar to other existing 5-fluorouracil products. The expected risks of Tolak (fluorouracil) Cream 4% are local, dermatologic effects at the application sites. The safety data reported in the studies in this application did not identify any other safety concerns beyond those expected local adverse events.

9.3.2 Required Phase 4 Commitments

No post-marketing commitments are recommended.

9.3.3 Other Phase 4 Requests

The sponsor should submit the final study report for the long term safety study 050 by six months from the date of action for this application.

9.4 Labeling Review

Labeling negotiations are ongoing at the time of closure of this clinical review.

9.5 Comments to Applicant

Please submit the final study report for the long term safety study 050 by six months from the date of action for this application.

10. APPENDICES

Final Prescribing Information—pending.

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

/s/

David Kettl
5/1/2008 03:00:19 PM
MEDICAL OFFICER

Markham Luke
5/1/2008 03:24:47 PM
MEDICAL OFFICER
Concur with AP recommendation. See also CDTL review. CMC inspections pending.

Susan Walker
6/2/2008 05:19:16 PM
DIRECTOR
Issues pending final resolution include final labeling and finalization of other discipline reviews, including chemistry. An addendum to the medical officer review may be appropriate prior to agency action.