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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Product:	Tolak (fluorouracil) cream, 4%
Indication:	Actinic Keratosis
Applicant:	Hill Dermaceuticals, Inc.
Review Division:	DDDP
Reviewer:	Barbara Hill, PhD
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1 Executive Summary

1.1 Introduction

This NDA resubmission addresses the issues detailed in the Complete Response letter sent to the sponsor on June 22, 2009 for the original NDA submission. No nonclinical issues were identified in the Complete Response letter.

No nonclinical toxicology studies were conducted to support the original NDA submission or the NDA resubmission. The sponsor included literature references in the original NDA submission (submitted on August 20, 2007) that address the toxicology of fluorouracil. The information contained in these literature references is summarized in the appropriate sections of this document. In addition, nonclinical information from the Efudex cream label is incorporated into this review for reference purposes since the sponsor was able to generate a clinical bridge to Efudex cream. Therefore, this NDA is submitted as a 505(b)(2) submission.

1.2 Brief Discussion of Nonclinical Findings

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.

Numerous articles exist in the literature describing the mutagenicity of fluorouracil. Many of these articles indicate that fluorouracil has genotoxic effects in both mammalian and non-mammalian systems. It is not unexpected that compounds such as fluorouracil that have an effect on DNA, RNA and protein synthesis would have positive effects on mutagenicity and chromosomal damage.

Most of the literature studies conducted to address the carcinogenic potential of fluorouracil are inadequate. The studies suffered from a number of deficiencies such as small group sizes, low doses, incomplete histopathology and short duration of exposure. There is inadequate data available to determine the potential carcinogenic risk associated with fluorouracil. However, based on the strong genotoxicity signal noted in the literature, it is anticipated that fluorouracil would prove to be a carcinogenic agent in appropriately designed and conducted nonclinical carcinogenicity studies. The Division has determined that the treatment of actinic keratosis with topical fluorouracil is not a chronic indication due to the extensive irritation at the treatment site. Therefore, carcinogenicity studies are not needed for Tolak cream.

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

1.3 Recommendations

1.3.1 Approvability

NDA 22259 for Tolak cream is approvable from a Pharmacology/Toxicology perspective provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the Tolak cream label.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

It is recommended that the <u>underlined</u> wording be inserted into and the ~~strikeout~~ wording be deleted from the Tolak cream label reproduced below. The pharmacologic class designation for Tolak cream for the treatment of actinic keratosis is nucleoside metabolic inhibitor. A clean copy of the suggested wording for the nonclinical sections of the label is provided in Appendix 1.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
Tolak (fluorouracil) Cream, 4%, is a nucleoside metabolic inhibitor indicated for the topical treatment of actinic keratosis lesions of the face, ears, and scalp (1).

Reviewer's comments: This section is consistent with the information in the Efudex label. The Pharmacologic Class designation is appropriate.

4 CONTRAINDICATIONS
4.1 Pregnancy

Tolak Cream may cause fetal harm when administered during pregnancy and is contraindicated in women who are (b) (4) 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.

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(b) (4)

Animal reproduction studies have not been conducted with Tolak Cream. Fluorouracil administered parenterally has been shown to be teratogenic in mice, rats, and hamsters when given at doses equivalent to the usual human intravenous dose. However, the amount of fluorouracil absorbed systemically after topical administration to actinic keratosis is minimal [see *Clinical Pharmacology* (12.3) (b) (4) 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.

Reviewer's comments: The nonclinical information in paragraph 3 of this section is consistent with the information in the Efudex label. The clinical reviewer will comment on the adequacy of the information in the first and second paragraphs of this section.

(b) (4)

(b) (4)

[redacted]

Reviewer's comments: The sponsor attempted to modify Section 8 of the label to conform with PLLR. However, it has been determined that the Tolak cream label will not be revised to conform with PLLR at this time. Therefore, Section 8 of the Tolak cream label should contain the same information as contained in the Efudex cream label. The recommended edits to Section 8 of the Tolak cream label are made to make it consistent with the Efudex cream label. For a Pregnancy Category X drug, the animal data is contained in Section 4.1 of the label as described above.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

There is (b)(4) evidence (b)(4) that the metabolism of fluorouracil in the anabolic pathway blocks (b)(4) the methylation reaction of deoxyuridylic acid to thymidylic acid. In this manner, fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to (b)(4) create (b)(4) a thymine deficiency that provokes unbalanced growth and death of the cell. (b)(4) The effects of DNA and RNA deprivation are most marked on those cells that grow more rapidly and take up fluorouracil at a more rapid rate.

Reviewer's comments: This section has been modified to make it consistent with the information in the Efudex label.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil. Studies with the active ingredient of Tolak, fluorouracil, have shown mutagenic effects in in vitro and in vivo tests and impairment of fertility in in vivo animal studies.

Fluorouracil was positive in three in vitro cell neoplastic transformation assays. In the C3H/10T½ clone 8 mouse embryo cell system, the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed syngeneic mice.

Although no evidence for mutagenic activity of fluorouracil was observed in 3 studies utilizing the Ames test, mutagenic activity was observed in the survival count rec-assay with *Bacillus subtilis* and in the *Drosophila* wing-hair spot test. Fluorouracil produced petite mutations in *Saccharomyces cerevisiae* and demonstrated positive results in the micronucleus test using bone marrow cells of male mice.

Fluorouracil demonstrated clastogenic activity in vitro in Chinese hamster fibroblasts at concentrations of 1.0 and 2.0 µg/mL and was associated with chromatid gaps, breaks, and exchanges. In human lymphocytes, fluorouracil increased sister chromatid exchange in vitro. Additionally, an increase in numerical and structural chromosome aberrations have been observed in peripheral lymphocytes of patients treated with fluorouracil.

In rats, chromosomal abnormalities and changes in chromosome organization in spermatogonia have been observed after intraperitoneal administration of 125 to 250

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mg/kg of fluorouracil. Spermatogonial differentiation was also inhibited and resulted in transient infertility. Fluorouracil was inactive, however, at oral doses of 5 to 80 mg/kg/day in studies with a strain of mouse which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens. In female rats, fluorouracil administered intraperitoneally at doses of 25 and 50 mg/kg during the preovulatory phase of oogenesis resulted in a significant reduction in the incidence of fertile matings, a delay in the development of preimplantation and postimplantation embryos, an increased incidence of preimplantation lethality, and an induction of chromosomal anomalies in these embryos. In mice, single intravenous or intraperitoneal injections of fluorouracil were toxic to differentiated spermatogonia and spermatocytes (at 500 mg/kg) and produced abnormalities in spermatids (at 50 mg/kg).

Reviewer's comments: This section is consistent with the information in the Efudex label.

2 Drug Information

2.1 Drug

CAS Registry Number

51-21-8

Generic Name

Fluorouracil, 5-fluorouracil

Code Name

DL6025

Chemical Name

5-Fluoro-2,4(1H,3H)-Pyrimidinedione

Molecular Formula/Molecular Weight

$C_4H_3FN_2O_2$ / 130.1

Structure or Biochemical Description

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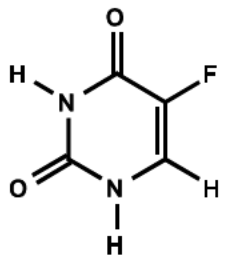

Pharmacologic Class

Nucleoside Metabolic Inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

1) IND 69,841 (Fluorouracil cream, 4%; actinic keratosis; DDDP)
2) NDA 16-765 [Fluoroplex (Fluorouracil) topical solution, 1%; actinic keratosis; DDDP; Approved 7/31/70]
3) NDA 16-988 [Fluoroplex (Fluorouracil) topical cream, 1%; actinic keratosis; DDDP; Approved 8/6/71]
4) NDA 16-831 [Efudex (Fluorouracil) topical cream, 5% and topical solution, 2 and 5%; actinic keratosis; DDDP; Approved 7/29/70]
5) NDA 20-985 [Carac (Fluorouracil) topical cream, 0.5%; actinic keratosis; DDDP; Approved 10/27/00]

2.3 Drug Formulation

The composition of Tolak cream is provided in the table below.

Ingredient	w/w%
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	

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(b) (4)

2.4 Comments on Novel Excipients

N/A

2.5 Comments on Impurities/Degradants of Concern

N/A

2.6 Proposed Clinical Population and Dosing Regimen

Tolak cream is to be applied topically once daily to actinic keratosis lesions of the face, ears and scalp for up to 4 weeks, as tolerated, in adults, eighteen years of age and older.

2.7 Regulatory Background

The original NDA submission for Tolak cream was received on August 20, 2007. A Complete Response letter was sent to the sponsor on June 22, 2009. The primary issues raised in the Complete Response letter concerned Product Quality (refer to the Complete Response letter for detailed information). This NDA resubmission addresses the issues raised in the Complete Response letter.

The sponsor is relying on literature studies to fulfill the nonclinical toxicology data needs for this drug product. In addition, the sponsor has conducted a clinical study to form a clinical bridge to Efudex cream. Therefore, this topical product has been developed by a 505(b)(2) regulatory pathway. Efudex cream 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.

3 Studies Submitted

3.1 Studies Reviewed

No nonclinical toxicology studies were conducted to support this NDA submission. The sponsor included literature references in the original NDA submission (submitted on August 20, 2007) that address the toxicology of fluorouracil. The information contained in these literature references is summarized in the appropriate sections of this document. In addition, nonclinical information from the Efudex cream label is incorporated into this review for reference purposes since the sponsor was able to generate a clinical bridge to Efudex cream.

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

Original NDA 22259 Pharmacology/Toxicology review

4 Pharmacology

4.1 Primary Pharmacology

The mechanism of action of fluorouracil has been extensively studied and is well known. Fluorouracil causes death of rapidly proliferating cells, primarily through the inhibition of DNA synthesis. To inhibit DNA synthesis, fluorouracil must first go through biochemical activation (i.e., metabolism) to form 5-fluoro-deoxyuridine monophosphate (FdUMP). This metabolite subsequently leads to the inhibition of thymidylate synthetase, an enzyme essential for DNA synthesis.

In another metabolic pathway, fluorouracil can be metabolized to 5-fluorouridine-triphosphate (FUTP). This metabolite can subsequently be incorporated into all species of RNA and affect many processes important to RNA function. Ultimately, these effects on RNA can lead to errors in protein synthesis that may contribute to cell death.

When female CD-1 mice were treated topically with 5% fluorouracil (Efudex cream) either prior to or after treatment with 7,12-demethybenz[a]anthracene, it was demonstrated that fluorouracil killed cycling cells in the epidermis, but not quiescent cells. Also, fluorouracil suppressed the usual hyperplastic response of epidermal cells to treatment with 12-O-tetradecanoylphorbol-13-acetate, reduced the number of epidermal basal cells counted in cross-sections of skin and suppressed DNA synthesis. These data provided evidence that rapid proliferation of epidermal cells is an important criterion of fluorouracil specificity.

In summary, fluorouracil has several mechanisms of action at the molecular level. It inhibits deoxyribonucleic acid (DNA) synthesis by competitively inhibiting thymidylate synthetase. To a lesser extent, fluorouracil may also interfere with ribonucleic acid (RNA) synthesis by its incorporation into RNA and by blocking uracil. These effects on

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DNA and RNA synthesis disrupt cell metabolism, leading to cell death. Effects are generally greater in rapidly dividing cells, which take up fluorouracil more rapidly during growth and division. As a cytotoxic agent, fluorouracil was first used systemically as antineoplastic therapy for a variety of tumors.

4.2 Secondary Pharmacology

N/A

4.3 Safety Pharmacology

No nonclinical safety pharmacology studies were conducted with fluorouracil. Based on the toxicity profile established for fluorouracil in the literature, no safety pharmacology studies are recommended for the Tolak cream, at this time.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Following parental or oral administration to rodents, fluorouracil is widely distributed, with larger amounts reported in bone marrow, small intestine, splenic red pulp, liver, bladder and kidney.[1,2] Selective uptake by tumor tissue has been reported but varies considerably from tumor to tumor.[3]

The distribution of fluorouracil was studied in male mice over a 2 week period using whole body autoradiography after intravenous injection of ^{14}C-labeled fluorouracil (1.0-1.3 mg/kg).[4] The highest concentrations were observed in the liver, kidney and bladder over the first 20 minutes. This is consistent with rapid metabolism and excretion of the drug. After four days, the highest radioactivity was in the pancreas, lymphoid tissue, intestine and bone marrow. Radioactivity continued to be found in the pancreas after 14 days.

Studies in rats, rabbits and monkeys have shown that fluorouracil is not bound to plasma protein.[5,6,7]

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[1] IRAC (1981) Monographs on the evaluation of carcinogenic risks of chemicals to humans: 5-fluorouracil. Lyon, France, World Health Organization, International Agency for Research on Cancer. 26: 217-235.
[2] Mossa MA, Osman AM, El-sayed M, El-aaser AA, Ismael N and El-merzabani MM (1992) Distribution and toxicity of 5-fluorouracil after intraperitoneal and anal submucosal administration. *J. Pharm. Belg.* 47: 129-134.
[3] IRAC (1981) Monographs on the evaluation of carcinogenic risks of chemicals to humans: 5-fluorouracil. Lyon, France, World Health Organization, International Agency for Research on Cancer. 26: 217-235.
[4] Appelgren L-E, Hamberger B and Theve NO (1979) The distribution of ^{14}C-labelled 5-fluorouracil in mice. *Front. Gastrointest. Res.* 5: 62-70.
[5] IRAC (1981) Monographs on the evaluation of carcinogenic risks of chemicals to humans: 5-fluorouracil. Lyon, France, World Health Organization, International Agency for Research on Cancer. 26: 217-235.
[6] Yamashita S, Nadai T, Sumi M and Suda Y (1994) Possible role of serum protein binding to improve drug disposition. *Int. J. Pharmaceutics* 108: 241-247.
[7] Bouke RS, West CR, Chheda G and Tower DB (1973) Kinetics of entry and distribution of 5-fluorouracil in cerebrospinal fluid and brain following intravenous injection in a primate. *Cancer Res.* 33: 1735-1746.

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Following a controlled intravenous injection of ^{14}C-labeled fluorouracil solution into rhesus monkeys (5 ml at a rate of 1.1 ml/min), 91% of the dose was cleared from the vascular compartment within five minutes and 98% by one hour.[8] This is consistent with rapid distribution and elimination of fluorouracil. Approximately 0.13% of the dose was found in the cerebrospinal fluid (CSF) and 0.17% was found in the brain during the experimental hour.

The metabolic pathways of fluorouracil have been established previously in the literature. [9,10,11] Up to 80% of the fluorouracil dose is eliminated through metabolic degradation, primarily in the liver. The plasma half-life is 10-20 minutes in several species.

Both the catabolic and anabolic pathways have been described for fluorouracil metabolism. Catabolism of fluorouracil is analogous to that of uracil and proceeds largely in the liver to first form dihydrofluorouracil and then ultimately α-fluoro-β-alanine, urea, carbon dioxide and ammonia. During anabolism, fluorouracil can be converted to 5-fluoro-deoxyuridine monophosphate, which is an important inhibitor of thymidylate synthetase, an essential enzyme of DNA synthesis. This is the primary mechanism of action of fluorouracil in the treatment of various forms of cancer. Alternately, fluorouracil can undergo anabolism to fluorinated uridine, which can be incorporated into RNA after phosphorylation.

The kinetics and tissue distribution of α-fluoro-β-alanine, one of the major catabolites of fluorouracil was studied in rats following intravenous bolus administration of radiolabeled α-fluoro-β-alanine.[12] The major pathway of elimination of α-fluoro-β-alanine was urinary excretion with 70% of the administered dose excreted over 192 hours. Fecal excretion represented a minor elimination pathway for α-fluoro-β-alanine, with ~10% of the administered dose excreted over 192 hours. During the first 30 min, the highest levels of tissue radioactivity were found in the kidneys, liver, spleen, lungs and heart. Radioactivity was retained over longer time periods in the enterohepatic circulation, central nervous system, heart and skeletal muscle.

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[8] Bouke RS, West CR, Chheda G and Tower DB (1973) Kinetics of entry and distribution of 5-fluorouracil in cerebrospinal fluid and brain following intravenous injection in a primate. *Cancer Res.* 33: 1735-1746.
[9] Miller E (1971) The metabolism and pharmacology of 5-fluorouracil. *J. Surg. Oncol.* 3: 309-315.
[10] IRAC (1981) Monographs on the evaluation of carcinogenic risks of chemicals to humans: 5-fluorouracil. Lyon, France, World Health Organization, International Agency for Research on Cancer. 26: 217-235.
[11] Parker WB and Cheng YC (1990) Metabolism and mechanism of action of 5-fluorouracil. *Pharmacol. Ther.* 48: 381-395.
[12] Zhang R, Soong S-J, Liu T, Barnes S and Diasio RB (1992) Pharmacokinetics and tissue distribution of 2-fluoro-β-alanine in rats: potential relevance to toxicity pattern of 5-fluorouracil. *Drug Metab. Dispos.* 20: 113-119.

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Up to 80% of a parenteral or oral dose is metabolically degraded in mice and rats, primarily in the liver, while the remainder is excreted unchanged in the urine. [13] Metabolites can be excreted in the urine or bile, or as respiratory carbon dioxide. [14,15]

5.2 Toxicokinetics

N/A

6 General Toxicology

6.1 Single-Dose Toxicity

N/A

6.2 Repeat-Dose Toxicity

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.

The toxicities noted in the repeat dose nonclinical rat systemic toxicology studies contained in the RTECS database included weight loss or decreased weight gain, gastrointestinal effects, elevation in transaminase levels, changes in liver weight, changes in thymus weight, changes in spleen weight, changes in testicular weight, changes in serum composition (e.g., TP, bilirubin, cholesterol), normocytic anemia, changes in bone marrow, changes in erythrocyte (RBC) count, changes in leukocyte (WBC) count and changes in platelet count.

7 Genetic Toxicology

Numerous articles exist in the literature describing the mutagenicity of fluorouracil. Many of these articles indicate that fluorouracil has genotoxic effects in both mammalian and non-mammalian systems. The following information concerning fluorouracil genotoxicity is included in the Efudex cream label.

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[13] IRAC (1981) Monographs on the evaluation of carcinogenic risks of chemicals to humans: 5-fluorouracil. Lyon, France, World Health Organization, International Agency for Research on Cancer. 26: 217-235.
[14] Miller E (1971) The metabolism and pharmacology of 5-fluorouracil. *J. Surg. Oncol.* 3: 309-315.
[15] Zhang R, Soong S-J, Liu T, Barnes S and Diasio RB (1992) Pharmacokinetics and tissue distribution of 2-fluoro-β-alaninie in rats: potential relevance to toxicity pattern of 5-fluorouracil. *Drug Metab. Dispos.* 20: 113-119.

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"5-Fluorouracil was positive in three in vitro cell neoplastic transformation assays. In the C3H/10T ½ clone 8 mouse embryo cell system, the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed syngeneic mice.

While no evidence for mutagenic activity was observed in the Ames test (3 studies), fluorouracil has been shown to be mutagenic in the survival count rec-assay with *Bacillus subtilis* and in the Drosophilia wing-hair spot test. Fluorouracil produced petite mutations in *Saccharomyces cerevisiae* and was positive in the micronucleus test (bone marrow cells of male mice).

Fluorouracil was clastogenic in vitro (ie, chromatid gaps, breaks and exchanges) in Chinese hamster fibroblasts at concentrations of 1.0 and 2.0 µg/mL and has been shown to increase sister chromatid exchange in vitro in human lymphocytes. In addition, 5-fluorouracil has been reported to produce an increase in numerical and structural chromosome aberrations in peripheral lymphocytes of patients treated with this product."

In summary, fluorouracil was mutagenic and caused chromosomal damage in several in vivo and in vitro mammalian and non-mammalian systems. Negative results were observed in a few studies in the literature. However, the number of positive results far outweigh the number of negative results. It is not unexpected that compounds such as fluorouracil that have an effect on DNA, RNA and protein synthesis would have positive effects on mutagenicity and chromosomal damage.

No additional genetic toxicology studies are recommended for Tolak cream at this time.

8 Carcinogenicity

Most of the literature studies conducted to address the carcinogenic potential of fluorouracil are inadequate. The studies suffered from a number of deficiencies such as small group sizes, low doses, incomplete histopathology and short duration of exposure. There is inadequate data available to determine the potential carcinogenic risk associated with fluorouracil. However, based on the strong genotoxicity signal noted in the literature, it is anticipated that fluorouracil would prove to be a carcinogenic agent in appropriately designed and conducted nonclinical carcinogenicity studies. The Efudex cream label contains the following statement concerning the carcinogenicity associated with fluorouracil. "Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil."

The sponsor submitted a literature reference in the original IND submission and the NDA submission that was published in 2000. The literature reference describes a 2 year carcinogenicity study conducted in F344 rats with fluorouracil administered in the drinking water (Toyoda K, Shibutani M, Sato H, Uneyama C, Takahashi M, Hayashi Y, Hirose M. Lack of carcinogenicity and increased survival in F344 rats treated with

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fluorouracil for 2 years. Food Chem. Toxicol. 2000; 38: 187-193). Three doses of fluorouracil (0, 62 and 125 ppm) were administered to F344 rats (50/sex/dose) in the drinking water for 104 weeks (followed by a 7 week non-treatment period before final histopathological analysis). The actual daily fluorouracil doses administered in this study based on drinking water consumption were 0, 3.85 and 7.42 mg/kg/day for males and 0, 4.47 and 8.98 mg/kg/day for females. A complete histopathological analysis of all tissues/organs for all animals was performed in this study.

The article states that the doses used in the carcinogenicity study were based on a 13 week dose range finding rat toxicity study. Doses of 0, 31, 62, 125, 250 and 500 ppm in the drinking water were administered to rats for 13 weeks in the dose range finding study. The article states that no mortality was noted in this study and that body weight gains and consumption of drinking water were decreased dose dependently in this study. However, the extent of decrease was not provided in the article. Hypoplasia of the bone marrow was noted in all 500 ppm males and focal hemorrhage of the brain and spinal cord was noted in 250 and 500 ppm animals. The article states that based on these results, the maximum tolerable dose (MTD) of fluorouracil given in the drinking water was estimated as 125 ppm for F344 rats. It is not clear if 125 ppm would have been considered the MTD based on Agency criteria since the extent of treatment related effects on body weight gain were not provided in the literature reference.

No treatment related increase in mortality was noted in the 2 year rat carcinogenicity study. Body weight gain was slightly decreased in high dose animals (males: ↓3.4%; females: ↓3.7%) compared to control animals. However, no significant treatment related effect on body weight at the end of treatment was noted in this study. The survival rate was higher in high dose males and females compared to control animals. The increase in survival rate in the high dose group may have been due to the slight decrease in body weight gain rather than due to fluorouracil treatment. Histopathologically, a decreased incidence of islet cell adenomas was noted in low dose males and increased incidences of pituitary gland adenomas and pheochromocytomas was noted in low dose females. These effects reached statistical significance but did not demonstrate a dose dependent trend. A non-statistical increase in the incidence of hepatocellular adenomas was noted in high dose males (10/50) versus control males (4/50). It is not clear that any of these changes would be considered significant by Agency standards. Overall, the results of this experiment suggest that fluorouracil did not elicit an overt carcinogenic signal in rats when administered in drinking water, under the conditions of this study. The major flaw of this study is that the high dose group was not adequate due a lack of frank toxicity. However, since no overt carcinogenic signal was apparent in this study, it provides some degree of comfort that fluorouracil may not be carcinogenic after systemic exposure at low doses.

The Division has determined that the treatment of actinic keratosis with topical fluorouracil is not a chronic indication due to the extensive irritation at the treatment site. 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 Tolak

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cream.

9 Reproductive and Developmental Toxicology

The following information is included in the Efudex cream label for the reproductive and developmental toxicity potential of fluorouracil. Efudex cream is designated as Pregnancy Category X.

"Doses of 125 to 250 mg/kg, administered intraperitoneally, have been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats. Spermatogonial differentiation was also inhibited by fluorouracil, resulting in transient infertility. However, in studies with a strain of mouse, which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens, fluorouracil was inactive at oral doses of 5 to 80 mg/kg/day. In female rats, fluorouracil administered intraperitoneally at doses of 25 and 50 mg/kg during the preovulatory phase of oogenesis significantly reduced the incidence of fertile matings, delayed the development of preimplantation and postimplantation embryos, increased the incidence of preimplantation lethality and induced chromosomal anomalies in these embryos. Single dose intravenous and intraperitoneal injections of 5-fluorouracil have been reported to kill differentiated spermatogonia and spermatocytes (at 500 mg/kg) and to produce abnormalities in spermatids (at 50 mg/kg) in mice.

Animal reproduction studies have not been conducted with Efudex. Fluorouracil administered parenterally has been shown to be teratogenic in mice, rats, and hamsters when given at doses equivalent to the usual human intravenous dose; however, the amount of fluorouracil absorbed systemically after topical administration to actinic keratoses is minimal. 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 (ie, 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. Doses higher than 40 mg/kg resulted in abortion.

There are no adequate and well-controlled studies in pregnant women with either the topical or parenteral forms of fluorouracil. One birth defect (cleft lip and palate) has been reported in the newborn of a patient using Efudex as recommended. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when Efudex was applied to mucous membrane areas. Multiple birth defects have been reported in a fetus of a patient treated with intravenous fluorouracil."

No additional reproductive and developmental toxicology studies are recommended for the Tolak cream at this time.

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10 Special Toxicology Studies

It is known that repeat dose dermal administration of Efudex cream produces dermal irritation that starts with erythema and progresses to ulceration/necrosis dependent on the duration of use. The degree of dermal irritation elicited by Efudex cream is significantly increased under conditions of occlusion. Since it is known that Efudex cream can generate severe dermal irritation, it is assumed that Tolak cream will be a dermal irritant and an ocular irritant if inadvertent exposure to the eyes should occur. No nonclinical dermal or ocular irritation studies were recommended for Tolak cream.

It is known from a clinical perspective that Efudex cream has the potential to elicit a hypersensitivity reaction. The sponsor has conducted a clinical contact sensitization study with Tolak cream. This is more relevant than a nonclinical study for determining the potential for Tolak cream to elicit a sensitization reaction. Therefore, the need to conduct a nonclinical hypersensitivity test was waived for Tolak cream.

The sponsor has conducted clinical phototoxicity and photoallergenicity studies with Tolak cream per the Division's recommendation. The sponsor has included a warning in the Tolak cream label that states "Exposure to ultraviolet rays including sunlight should be minimized during and immediately following treatment with Tolak because the intensity of the reaction may be increased." This is adequate to address this concern and conduct of a nonclinical phototoxicity study with Tolak cream is not necessary.

No additional special toxicology studies are recommended for Tolak cream at this time.

11 Integrated Summary and Safety Evaluation

The sponsor generated a clinical bridge to Efudex cream which allows the Agency to use our findings of safety to support Tolak cream. In addition, the sponsor is relying on literature studies to fulfill the nonclinical toxicology data needs for this drug product. Therefore, Tolak cream was developed by a 505(b)(2) regulatory pathway. The nonclinical information contained in the Efudex cream label and the submitted literature references has been incorporated into the Tolak cream label.

12 Appendix/Attachments

Appendix 1: Clean copy of recommended wording for Nonclinical sections of the Tolak cream label

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Tolak (fluorouracil) Cream, 4%, is a nucleoside metabolic inhibitor indicated for the topical treatment of actinic keratosis lesions of the face, ears, and scalp (1).

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4 CONTRAINDICATIONS
4.1 Pregnancy

Tolak Cream 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)

Animal reproduction studies have not been conducted with Tolak Cream. Fluorouracil administered parenterally has been shown to be teratogenic in mice, rats, and hamsters when given at doses equivalent to the usual human intravenous dose. However, the amount of fluorouracil absorbed systemically after topical administration to actinic keratosis 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.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Teratogenic Effects: Pregnancy Category X [see *Contraindications* (4.1)].

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this manner, fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency that provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells that grow more rapidly and take up fluorouracil at a more rapid rate.

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil. Studies with the active ingredient of Tolak, fluorouracil, have shown mutagenic effects in in vitro and in vivo tests and impairment of fertility in in vivo animal studies.

Fluorouracil was positive in three in vitro cell neoplastic transformation assays. In the C3H/10T½ clone 8 mouse embryo cell system, the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed syngeneic mice.

Although no evidence for mutagenic activity of fluorouracil was observed in 3 studies utilizing the Ames test, mutagenic activity was observed in the survival count rec-assay with *Bacillus subtilis* and in the *Drosophila* wing-hair spot test. Fluorouracil produced petite mutations in *Saccharomyces cerevisiae* and demonstrated positive results in the micronucleus test using bone marrow cells of male mice.

Fluorouracil demonstrated clastogenic activity in vitro in Chinese hamster fibroblasts at concentrations of 1.0 and 2.0 µg/mL and was associated with chromatid gaps, breaks, and exchanges. In human lymphocytes, fluorouracil increased sister chromatid exchange in vitro. Additionally, an increase in numerical and structural chromosome aberrations have been observed in peripheral lymphocytes of patients treated with fluorouracil.

In rats, chromosomal abnormalities and changes in chromosome organization in spermatogonia have been observed after intraperitoneal administration of 125 to 250 mg/kg of fluorouracil. Spermatogonial differentiation was also inhibited and resulted in transient infertility. Fluorouracil was inactive, however, at oral doses of 5 to 80 mg/kg/day in studies with a strain of mouse which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens. In female rats, fluorouracil administered intraperitoneally at doses of 25 and 50 mg/kg during the preovulatory phase of oogenesis resulted in a significant reduction in the incidence of fertile matings, a delay in the development of preimplantation and postimplantation embryos, an increased incidence of preimplantation lethality, and an induction of chromosomal anomalies in these embryos. In mice, single intravenous or intraperitoneal injections of fluorouracil were toxic to differentiated spermatogonia and spermatocytes (at 500 mg/kg) and produced abnormalities in spermatids (at 50 mg/kg).

Reference ID: 3802318

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/s/

BARBARA A HILL
08/05/2015

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-259**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**August 20, 2007**
PRODUCT:	**5-Fluorouracil cream, 4.0%**
INTENDED CLINICAL POPULATION:	**Actinic Keratosis**
SPONSOR:	**Hill Dermaceuticals, Inc.**
DOCUMENTS REVIEWED:	**Paper CTD NDA submission; Modules 1, 2 and 4**
REVIEW DIVISION:	**Division of Dermatology and Dental Products (HFD-540)**
PHARM/TOX REVIEWER:	**Barbara Hill, Ph.D.**
PHARM/TOX SUPERVISOR:	**Paul Brown, Ph.D.**
DIVISION DIRECTOR:	**Susan Walker, M.D.**
PROJECT MANAGER:	**Catherine Carr**

Date of review submission to Division File System (DFS): 3-25-08

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability – The 4% 5-fluorouracil cream NDA is approvable from a pharmacological/toxicological perspective.

B. Recommendation for nonclinical studies – None

C. Recommendations on labeling – Recommended wording for the nonclinical portions of the label are provided in the "Suggested Labeling" section located at the end of this review.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings – The nonclinical toxicology of systemically (oral, intravenous, etc) or topically administered 5-fluorouracil has been established previously in the literature. The main adverse effects noted with parenterally or orally administered 5-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.

Numerous articles exist in the literature describing the mutagenicity of 5-fluorouracil. Many of these articles indicate that 5-fluorouracil has genotoxic effects in both mammalian and non-mammalian systems. It is not unexpected that compounds such as 5-fluorouracil that have an effect on DNA, RNA and protein synthesis would have positive effects on mutagenicity and chromosomal damage.

Most of the literature studies conducted to address the carcinogenic potential of 5-fluorouracil are inadequate. The studies suffered from a number of deficiencies such as small group sizes, low doses, incomplete histopathology and short duration of exposure. There is inadequate data available to determine the potential carcinogenic risk associated with 5-fluorouracil. However, based on the strong genotoxicity signal noted in the literature, it is anticipated that 5-fluorouracil would prove to be a carcinogenic agent in appropriately designed and conducted nonclinical carcinogenicity studies. The Division has determined that the treatment of actinic keratosis with 5-fluorouarcil is not a chronic indication. Therefore, carcinogenicity studies are not needed for the 4% 5-fluorouracil cream.

Systemic 5-fluorouracil treatment elicited teratogenic effects in mice, rats, hamsters and monkeys and embryoletality in hamsters and monkeys. Systemic 5-fluorouracil treatment induced chromosomal aberrations and changes in chromosome organization

of spermatogonia in rats which resulted in transient infertility in male rats. Systemic 5-fluorouracil treatment elicited negative effects on female fertility in rats (significantly reduced the incidence of fertile matings, delayed the development of preimplantation and postimplantation embryos, increased the incidence of preimplantation lethality and induced chromosomal anomalies in these embryos). Teratogenic effects have been noted in humans after topical application of Efudex (5-fluorouracil, 5%) cream and systemic administration of 5-fluorouracil. The 4% fluorouracil cream should be labeled as Pregnancy Category X to mimic the Pregnancy Category designation for Efudex cream.

B. Pharmacologic activity – Antimetabolite

C. Nonclinical safety issues relevant to clinical use – None at this time

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

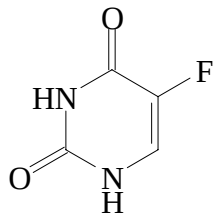
NDA number: 22-259
Review number: 1
Sequence number/date/type of submission: 000 / 8-20-07 / Original NDA submission
Information to sponsor: No
Sponsor and/or agent: Hill Dermaceuticals, Inc.
2650 South Mellonville Avenue
Sanford, FL 32773-9311

Manufacturer for drug substance: (b) (4)

Reviewer name: Barbara Hill
Division name: Dermatologic and Dental Drug Products
HFD #: HFD-540
Review completion date: 2-14-08

Drug:

Trade name: N/A
Generic name: 5-Fluorouracil cream, 4.0%
Code name: DL 6025
Chemical name: 5-Fluoro-2,4(1H,3H)-Pyrimidinedione
CAS registry number: 51-21-8
Molecular formula/molecular weight: $C_4H_3FN_2O_2$ / 130. (b) (4)
Structure:



Relevant INDs/NDAs/DMFs:

1) IND 69,841 (Fluorouracil cream, 4%; actinic keratosis; HFD-540)
1) NDA 16-765 (Fluoroplex {Fluorouracil} 1% topical solution; actinic keratosis; HFD-540; Approved 7/31/70)
2) NDA 16-988 (Fluoroplex {Fluorouracil} 1% topical cream; actinic keratosis; HFD-540; Approved 8/6/71)
3) NDA 16-831 (Efudex {Fluorouracil} 5% topical cream and 2 and 5% topical solution; actinic keratosis; HFD-540; Approved 7/29/70)

4) NDA 20-985 (Carac {Fluorouracil} 0.5% topical cream; actinic keratosis; HFD-540; Approved 10/27/00)

Drug class: Antimetabolite

Intended clinical population: Treatment of actinic keratosis

Clinical formulation:

The composition of the 4.0% 5-fluorouracil cream is provided in the table below.

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)

Route of administration: Topical

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-259 are owned by Hill Dermaceuticals, Inc. or are data for which Hill Dermaceuticals, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22-259 that Hill Dermaceuticals, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Hill Dermaceuticals, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-259.

Background:

A pre-IND meeting was conducted with the sponsor on August 16, 2004. The original IND application was submitted on November 12, 2004. An End of Phase 2 meeting was conducted on November 21, 2005. A pre-NDA meeting was conducted on April 23, 2007. The sponsor is developing the 4% 5-fluorouracil cream for the treatment of actinic keratosis. This NDA submission is a paper CTD submission. In addition, the sponsor has submitted an electronic copy of the draft label for the 4% 5-fluorouracil cream in PLR format as a word document. The sponsor is relying on literature studies to fulfill the nonclinical toxicology data needs for this drug product. In addition, the sponsor has conducted a clinical study to form a clinical bridge to Efudex cream (5% 5-fluorouracil cream). Therefore, the NDA submission is a 505(b)(2) NDA.

5-Fluorouracil has been used for over 30 years as an antineoplastic agent administered by the parental (intravenous) route. It has also been used for almost 30 years in topical formulations of 1 to 5% for the treatment of actinic keratosis (i.e., Efudex® and Fluroplex®). Only the 5% strength of the Efudex cream or solution formulation is recommended for the treatment of superficial basal cell carcinoma.

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. 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 most frequent adverse reactions reported for Efudex occur locally and include burning, crusting, allergic contact dermatitis, erosions, erythema, hyperpigmentation, irritation, pain, photosensitivity, pruritus, scarring, rash, soreness and ulceration. Ulcerations, other local reactions, cases of miscarriage and a birth defect (ventricular septal defect) have been reported when Efudex was applied to mucous membrane areas. Leukocytosis is the most frequent hematological side effect. Other adverse reactions listed in the Efudex label include the following.

Central Nervous System: Emotional upset, insomnia, irritability.

Gastrointestinal: Medicinal taste, stomatitis.

Hematological: Eosinophilia, thrombocytopenia, toxic granulation.

Integumentary: Alopecia, blistering, bullous pemphigoid, discomfort, ichthyosis, scaling, suppuration, swelling, telangiectasia, tenderness, urticaria, skin rash.

Special Senses: Conjunctival reaction, corneal reaction, lacrimation, nasal irritation.

Miscellaneous: Herpes simplex.

Phase 3 clinical studies have been conducted in actinic keratosis patients with the 4% 5-fluorouracil cream with once daily administration. The sponsor anticipates that the slightly lower concentration (4% versus 5%) and less frequent application (once daily versus twice daily for 4 weeks) for the 4% fluorouracil cream will generate a similar degree of efficacy compared to Effudex with lower local adverse events. Refer to Clinical review for an analysis of the conducted clinical studies for the 4% 5-fluorouracil cream.

Studies reviewed within this submission:

No nonclinical toxicology studies were conducted to support this NDA submission. The sponsor included literature references that address the toxicology of 5-fluorouracil. The information contained in these literature references is summarized in the appropriate sections of this document. In addition, nonclinical information from the Efudex cream label is incorporated into this review for reference purposes since the sponsor was able to generate a clinical bridge to Efudex cream.

Studies not reviewed within this submission: N/A

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

The mechanism of action of 5-fluorouracil has been extensively studied and is well known. 5-Fluorouracil causes death of rapidly proliferating cells, primarily through the

inhibition of DNA synthesis. To inhibit DNA synthesis, 5-fluorouracil must first go through biochemical activation (i.e., metabolism) to form 5-fluoro-deoxyuridine monophosphate (FdUMP). This metabolite subsequently leads to the inhibition of thymidylate synthetase, an enzyme essential for DNA synthesis.

In another metabolic pathway, 5-fluorouracil can be metabolized to 5-fluorouridine-triphosphate (FUTP). This metabolite can subsequently be incorporated into all species of RNA and affect many processes important to RNA function. Ultimately, these effects on RNA can lead to errors in protein synthesis that may contribute to cell death.

When female CD-1 mice were treated topically with 5% 5-fluorouracil (Efudex cream) either prior to or after treatment with 7,12-demethybenz[a]anthracene, it was demonstrated that 5-fluorouracil killed cycling cells in the epidermis, but not quiescent cells. Also, 5-fluorouracil suppressed the usual hyperplastic response of epidermal cells to treatment with 12-O-tetradecanoylphorbol-13-acetate, reduced the number of epidermal basal cells counted in cross-sections of skin and suppressed DNA synthesis. These data provided evidence that rapid proliferation of epidermal cells is an important criterion of 5-fluorouracil specificity.

In summary, 5-fluorouracil has several mechanisms of action at the molecular level. It inhibits deoxyribonucleic acid (DNA) synthesis by competitively inhibiting thymidylate synthetase. To a lesser extent, 5-fluorouracil may also interfere with ribonucleic acid (RNA) synthesis by its incorporation into RNA and by blocking uracil. These effects on DNA and RNA synthesis disrupt cell metabolism, leading to cell death. Effects are generally greater in rapidly dividing cells, which take up 5-fluorouracil more rapidly during growth and division. As a cytotoxic agent, 5-fluorouracil was first used systemically as antineoplastic therapy for a variety of tumors.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Refer to brief summary

Drug activity related to proposed indication: Refer to brief summary

2.6.2.3 Secondary pharmacodynamics – N/A

2.6.2.4 Safety pharmacology

No nonclinical safety pharmacology studies were conducted with 5-fluorouracil. Based on the toxicity profile established for 5-fluorouracil in the literature, no safety pharmacology studies are recommended for the 4% 5-fluorouracil cream, at this time.

2.6.2.5 Pharmacodynamic drug interactions – N/A

2.6.3 PHARMACOLOGY TABULATED SUMMARY – N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Following parental or oral administration to rodents, 5-fluorouracil is widely distributed, with larger amounts reported in bone marrow, small intestine, splenic red pulp, liver, bladder and kidney.[1,2] Selective uptake by tumor tissue has been reported but varies considerably from tumor to tumor.[3]

The distribution of 5-fluorouracil was studied in male mice over a 2 week period using whole body autoradiography after intravenous injection of ^{14}C-labeled 5-fluorouracil (1.0-1.3 mg/kg).[4] The highest concentrations were observed in the liver, kidney and bladder over the first 20 minutes. This is consistent with rapid metabolism and excretion of the drug. After four days, the highest radioactivity was in the pancreas, lymphoid tissue, intestine and bone marrow. Radioactivity continued to be found in the pancreas after 14 days.

Studies in rats, rabbits and monkeys have shown that 5-fluorouracil is not bound to plasma protein.[5,6,7]

Following a controlled intravenous injection of ^{14}C-labeled 5-fluorouracil solution into rhesus monkeys (5 ml at a rate of 1.1 ml/min), 91% of the dose was cleared from the vascular compartment within five minutes and 98% by one hour.[8] This is consistent with rapid distribution and elimination of 5-fluorouracil. Approximately 0.13% of the dose was found in the cerebrospinal fluid (CSF) and 0.17% was found in the brain during the experimental hour.

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[1] IRAC (1981) Monographs on the evaluation of carcinogenic risks of chemicals to humans: 5-fluorouracil. Lyon, France, World Health Organization, International Agency for Research on Cancer. 26: 217-235.
[2] Mossa MA, Osman AM, El-sayed M, El-aaser AA, Ismael N and El-merzabani MM (1992) Distribution and toxicity of 5-fluorouracil after intraperitoneal and anal submucosal administration. *J. Pharm. Belg.* 47: 129-134.
[3] IRAC (1981) Monographs on the evaluation of carcinogenic risks of chemicals to humans: 5-fluorouracil. Lyon, France, World Health Organization, International Agency for Research on Cancer. 26: 217-235.
[4] Appelgren L-E, Hamberger B and Theve NO (1979) The distribution of ^{14}C-labelled 5-fluorouracil in mice. *Front. Gastrointest. Res.* 5: 62-70.
[5] IRAC (1981) Monographs on the evaluation of carcinogenic risks of chemicals to humans: 5-fluorouracil. Lyon, France, World Health Organization, International Agency for Research on Cancer. 26: 217-235.
[6] Yamashita S, Nadai T, Sumi M and Suda Y (1994) Possible role of serum protein binding to improve drug disposition. *Int. J. Pharmaceutics* 108: 241-247.
[7] Bouke RS, West CR, Chheda G and Tower DB (1973) Kinetics of entry and distribution of 5-fluorouracil in cerebrospinal fluid and brain following intravenous injection in a primate. *Cancer Res.* 33: 1735-1746.
[8] Bouke RS, West CR, Chheda G and Tower DB (1973) Kinetics of entry and distribution of 5-fluorouracil in cerebrospinal fluid and brain following intravenous injection in a primate. *Cancer Res.* 33: 1735-1746.

The metabolic pathways of 5-fluorouracil have been established previously in the literature. [9,10,11] Up to 80% of the 5-fluorouracil dose is eliminated through metabolic degradation, primarily in the liver. The plasma half-life is 10-20 minutes in several species.

Both the catabolic and anabolic pathways have been described for 5-fluorouracil metabolism. Catabolism of 5-fluorouracil is analogous to that of uracil and proceeds largely in the liver to first form dihydrofluorouracil and then ultimately α-fluoro-β-alanine, urea, carbon dioxide and ammonia. During anabolism, 5-fluorouracil can be converted to 5-fluoro-deoxyuridine monophosphate, which is an important inhibitor of thymidylate synthetase, an essential enzyme of DNA synthesis. This is the primary mechanism of action of 5-fluorouracil in the treatment of various forms of cancer. Alternately, 5-fluorouracil can undergo anabolism to fluorinated uridine, which can be incorporated into RNA after phosphorylation.

The kinetics and tissue distribution of α-fluoro-β-alanine, one of the major catabolites of 5-fluorouracil was studied in rats following intravenous bolus administration of radiolabeled α-fluoro-β-alanine.[12] The major pathway of elimination of α-fluoro-β-alanine was urinary excretion with 70% of the administered dose excreted over 192 hours. Fecal excretion represented a minor elimination pathway for α-fluoro-β-alanine, with ~10% of the administered dose excreted over 192 hours. During the first 30 min, the highest levels of tissue radioactivity were found in the kidneys, liver, spleen, lungs and heart. Radioactivity was retained over longer time periods in the enterohepatic circulation, central nervous system, heart and skeletal muscle.

Up to 80% of a parenteral or oral dose is metabolically degraded in mice and rats, primarily in the liver, while the remainder is excreted unchanged in the urine. [13] Metabolites can be excreted in the urine or bile, or as respiratory carbon dioxide. [14,15]

2.6.4.2 Methods of Analysis – N/A

2.6.4.3 Absorption – Refer to brief summary

2.6.4.4 Distribution – Refer to brief summary

2.6.4.5 Metabolism – Refer to brief summary

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[9] Miller E (1971) The metabolism and pharmacology of 5-fluorouracil. *J. Surg. Oncol.* 3: 309-315.
[10] IRAC (1981) Monographs on the evaluation of carcinogenic risks of chemicals to humans: 5-fluorouracil. Lyon, France, World Health Organization, International Agency for Research on Cancer. 26: 217-235.
[11] Parker WB and Cheng YC (1990) Metabolism and mechanism of action of 5-fluorouracil. *Pharmacol. Ther.* 48: 381-395.
[12] Zhang R, Soong S-J, Liu T, Barnes S and Diasio RB (1992) Pharmacokinetics and tissue distribution of 2-fluoro-β-alanine in rats: potential relevance to toxicity pattern of 5-fluorouracil. *Drug Metab. Dispos.* 20: 113-119.
[13] IRAC (1981) Monographs on the evaluation of carcinogenic risks of chemicals to humans: 5-fluorouracil. Lyon, France, World Health Organization, International Agency for Research on Cancer. 26: 217-235.
[14] Miller E (1971) The metabolism and pharmacology of 5-fluorouracil. *J. Surg. Oncol.* 3: 309-315.
[15] Zhang R, Soong S-J, Liu T, Barnes S and Diasio RB (1992) Pharmacokinetics and tissue distribution of 2-fluoro-β-alaninie in rats: potential relevance to toxicity pattern of 5-fluorouracil. *Drug Metab. Dispos.* 20: 113-119.

2.6.4.6 Excretion – Refer to brief summary

2.6.4.7 Pharmacokinetic drug interactions – N/A

2.6.4.8 Other Pharmacokinetic Studies – N/A

2.6.4.9 Discussion and Conclusions

No nonclinical pharmacokinetic studies are recommended for the 4% 5-fluorouracil cream at this time.

2.6.4.10 Tables and figures to include comparative TK summary – N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY – N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

The nonclinical toxicology of systemically (oral, intravenous, etc) or topically administered 5-fluorouracil has been established previously in the literature. The main adverse effects noted with parenterally or orally administered 5-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.

The toxicities noted in the repeat dose nonclinical rat systemic toxicology studies contained in the RTECS database included weight loss or decreased weight gain, gastrointestinal effects, elevation in transaminase levels, changes in liver weight, changes in thymus weight, changes in spleen weight, changes in testicular weight, changes in serum composition (e.g., TP, bilirubin, cholesterol), normocytic anemia, changes in bone marrow, changes in erythrocyte (RBC) count, changes in leukocyte (WBC) count and changes in platelet count.

Genetic toxicology:

Numerous articles exist in the literature describing the mutagenicity of 5-fluorouracil. Many of these articles indicate that 5-fluorouracil has genotoxic effects in both mammalian and non-mammalian systems. The following information concerning 5-fluorouracil genotoxicity is included in the Efudex cream label.

“5-Fluorouracil was positive in three in vitro cell neoplastic transformation assays. In the

C3H/10T ½ clone 8 mouse embryo cell system, the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed syngeneic mice.

While no evidence for mutagenic activity was observed in the Ames test (3 studies), fluorouracil has been shown to be mutagenic in the survival count rec-assay with *Bacillus subtilis* and in the Drosophilia wing-hair spot test. Fluorouracil produced petite mutations in *Saccharomyces cerevisiae* and was positive in the micronucleus test (bone marrow cells of male mice).

Fluorouracil was clastogenic in vitro (ie, chromatid gaps, breaks and exchanges) in Chinese hamster fibroblasts at concentrations of 1.0 and 2.0 µg/mL and has been shown to increase sister chromatid exchange in vitro in human lymphocytes. In addition, 5-fluorouracil has been reported to produce an increase in numerical and structural chromosome aberrations in peripheral lymphocytes of patients treated with this product."

In summary, 5-fluorouracil was mutagenic and caused chromosomal damage in several in vivo and in vitro mammalian and non-mammalian systems. Negative results were observed in a few studies in the literature. However, the number of positive results far outweigh the number of negative results. It is not unexpected that compounds such as 5-fluorouracil that have an effect on DNA, RNA and protein synthesis would have positive effects on mutagenicity and chromosomal damage.

No additional genetic toxicology studies are recommended for the 4% 5-fluorouracil cream at this time.

Carcinogenicity:

Most of the literature studies conducted to address the carcinogenic potential of 5-fluorouracil are inadequate. The studies suffered from a number of deficiencies such as small group sizes, low doses, incomplete histopathology and short duration of exposure. There is inadequate data available to determine the potential carcinogenic risk associated with 5-fluorouracil. However, based on the strong genotoxicity signal noted in the literature, it is anticipated that 5-fluorouracil would prove to be a carcinogenic agent in appropriately designed and conducted nonclinical carcinogenicity studies. The Efudex cream label contains the following statement concerning the carcinogenicity associated with 5- fluorouracil. "Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil."

The sponsor submitted a literature reference in the original IND submission and the NDA submission that was published in 2000. The literature reference describes a 2 year carcinogenicity study conducted in F344 rats with 5-fluororacil administered in the drinking water (Toyoda K, Shibutani M, Sato H, Uneyama C, Takahashi M, Hayashi Y, Hirose M. Lack of carcinogenicity and increased survival in F344 rats treated with 5-fluorouracil for 2 years. Food Chem. Toxicol. 2000; 38: 187-193). Three doses of 5-fluorouracil (0, 62 and 125 ppm) were administered to F344 rats (50/sex/dose) in the drinking water for 104 weeks (followed by a 7 week non-treatment period before final histopathological analysis). The actual daily 5-

fluorouracil doses administered in this study based on drinking water consumption were 0, 3.85 and 7.42 mg/kg/day for males and 0, 4.47 and 8.98 mg/kg/day for females. A complete histopathological analysis of all tissues/organs for all animals was performed in this study.

The article states that the doses used in the carcinogenicity study were based on a 13 week dose range finding rat toxicity study. Doses of 0, 31, 62, 125, 250 and 500 ppm in the drinking water were administered to rats for 13 weeks in the dose range finding study. The article states that no mortality was noted in this study and that body weight gains and consumption of drinking water were decreased dose dependently in this study. However, the extent of decrease was not provided in the article. Hypoplasia of the bone marrow was noted in all 500 ppm males and focal hemorrhage of the brain and spinal cord was noted in 250 and 500 ppm animals. The article states that based on these results, the maximum tolerable dose (MTD) of 5-fluorouracil given in the drinking water was estimated as 125 ppm for F344 rats. It is not clear if 125 ppm would have been considered the MTD based on Agency criteria since the extent of treatment related effects on body weight gain were not provided in the literature reference.

No treatment related increase in mortality was noted in the 2 year rat carcinogenicity study. Body weight gain was slightly decreased in high dose animals (males: ↓3.4%; females: ↓3.7%) compared to control animals. However, no significant treatment related effect on body weight at the end of treatment was noted in this study. The survival rate was higher in high dose males and females compared to control animals. The increase in survival rate in the high dose group may have been due to the slight decrease in body weight gain rather than due to 5-fluorouracil treatment. Histopathologically, a decreased incidence of islet cell adenomas was noted in low dose males and increased incidences of pituitary gland adenomas and pheochromocytomas was noted in low dose females. These effects reached statistical significance but did not demonstrate a dose dependent trend. A non-statistical increase in the incidence of hepatocellular adenomas was noted in high dose males (10/50) versus control males (4/50). It is not clear that any of these changes would be considered significant by Agency standards. Overall, the results of this experiment suggest that 5-fluorouracil did not elicit an overt carcinogenic signal in rats when administered in drinking water, under the conditions of this study. The major flaw of this study is that the high dose group was not adequate due a lack of frank toxicity. However, since no overt carcinogenic signal was apparent in this study, it provides some degree of comfort that 5- fluorouracil may not be carcinogenic after systemic exposure at low doses.

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.

No carcinogenicity studies are recommended for the 4% 5-fluorouracil cream at this time.

Reproductive toxicology:

The following information is included in the Efudex cream label for the reproductive and developmental toxicity potential of 5-fluorouracil. Efudex cream is designated as Pregnancy Category X.

"Doses of 125 to 250 mg/kg, administered intraperitoneally, have been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats. Spermatogonial differentiation was also inhibited by fluorouracil, resulting in transient infertility. However, in studies with a strain of mouse, which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens, fluorouracil was inactive at oral doses of 5 to 80 mg/kg/day. In female rats, fluorouracil administered intraperitoneally at doses of 25 and 50 mg/kg during the preovulatory phase of oogenesis significantly reduced the incidence of fertile matings, delayed the development of preimplantation and postimplantation embryos, increased the incidence of preimplantation lethality and induced chromosomal anomalies in these embryos. Single dose intravenous and intraperitoneal injections of 5-fluorouracil have been reported to kill differentiated spermatogonia and spermatocytes (at 500 mg/kg) and to produce abnormalities in spermatids (at 50 mg/kg) in mice.

Animal reproduction studies have not been conducted with Efudex. Fluorouracil administered parenterally has been shown to be teratogenic in mice, rats, and hamsters when given at doses equivalent to the usual human intravenous dose; however, the amount of fluorouracil absorbed systemically after topical administration to actinic keratoses is minimal. 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 (ie, 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. Doses higher than 40 mg/kg resulted in abortion.

There are no adequate and well-controlled studies in pregnant women with either the topical or parenteral forms of fluorouracil. One birth defect (cleft lip and palate) has been reported in the newborn of a patient using Efudex as recommended. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when Efudex was applied to mucous membrane areas. Multiple birth defects have been reported in a fetus of a patient treated with intravenous fluorouracil."

No additional reproductive and developmental toxicology studies are recommended for the 4% 5-fluorouracil cream at this time.

Special toxicology:

It is known that repeat dose dermal administration of Efudex cream produces dermal irritation that starts with erythema and progresses to ulceration/necrosis dependent on the

duration of use. The degree of dermal irritation elicited by Efudex cream is significantly increased under conditions of occlusion. Since it is known that Efudex cream can generate severe dermal irritation, it is assumed that the 4% 5-fluorouracil cream will be a dermal irritant and an ocular irritant if inadvertent exposure to the eyes should occur. No nonclinical dermal or ocular irritation studies were recommended for the 4% 5- fluorouracil cream.

It is known from a clinical perspective that Efudex cream has the potential to elicit a hypersensitivity reaction. The sponsor has conducted a clinical contact sensitization study with the 4% 5-fluorouracil cream. This is more relevant than a nonclinical study for determining the potential for 4% 5-fluorouracil cream to elicit a sensitization reaction. Therefore, the need to conduct a nonclinical hypersensitivity test was waived for the 4% 5-fluorouracil cream.

The sponsor has conducted clinical phototoxicity and photoallergenicity studies per the Division's recommendation. The sponsor included a UV-VIS spectrum (200 – 700 nm) for the 4% 5-fluorouracil cream in the End of Phase 2 briefing document that demonstrated a rather large shoulder absorbance in the 290 – 320 nm range. Normally, this would trigger the need for nonclinical photoirritation and clinical phototoxicity and photoallergenicity studies.

However, it is known that Efudex cream can elicit a photoirritation response and a warning is contained in the Efudex label that addresses this issue. The sponsor incorporated the same warning in the 4% 5-fluorouracil cream investigator's brochure. During the End of Phase 2 and pre-NDA meetings the following Pharmacology/Toxicology comment was relayed to the sponsor.

"The need for a nonclinical photoirritation study is waived for the 4% 5-fluorouracil cream since the sponsor is willing to incorporate a warning statement in the "Investigator's Brochure" similar to the one contained in the Efudex label; (b) (4) [redacted]." It is recommended that a similar warning be incorporated in the label for the 4% 5-fluorouracil cream if approved."

The purpose of a nonclinical photoirritation study is to determine if there is a potential concern. It is has been previously established that a photoirritation concern is apparent for the Efudex cream. Therefore, it would also be a concern for the 4% 5-fluorouracil cream and the need for a nonclinical photoirritation study was waived since the sponsor provided an appropriate warning in the "Investigator's Brochure". The clinical review team determined that phototoxicity and photoallergencity studies are required for the 4% 5-fluorouracil cream. The results of these studies are incorporated into the 4% 5-fluorouracil cream label.

No additional special toxicology studies are recommended for the 4% 5-fluorouracil cream at this time.

2.6.6.2 Single-dose toxicity – N/A

2.6.6.3 Repeat-dose toxicity – N/A

2.6.6.4 Genetic toxicology – N/A

2.6.6.5 Carcinogenicity – N/A

2.6.6.6 Reproductive and developmental toxicology – N/A

2.6.6.7 Local tolerance – N/A

2.6.6.8 Special toxicology studies – N/A

2.6.6.9 Discussion and Conclusions

The 4% 5-fluorouracil cream NDA is a 505(b)(2) submission since the sponsor generated a clinical 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.

2.6.6.10 Tables and Figures – N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY – N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Based on the nonclinical data available for 5-fluorouracil, NDA 22-259 for the 4% 5-fluorouracil cream drug product is approvable from a pharmacology/toxicology perspective provided that the recommended changes in the label discussed in the next section are incorporated into the 4% 5-fluorouracil cream drug product label.

Unresolved toxicology issues (if any):

There are no unresolved toxicology issues for NDA 22-259, at this time.

Recommendations:

It is recommended that the suggested labeling changes provided in the next section be incorporated into the 4% 5-fluorouracil cream drug product label.

Suggested labeling:

The sponsor included a label for the 4% 5-fluorouracil cream drug product in the new PLR format in the NDA submission. The nonclinical portions of the 4% 5-fluorouracil cream drug

product label are provided below. It is recommended that the highlighted wording be inserted into and the ~~strikeout~~ wording be deleted from the sections of the 4% 5-fluorouracil cream drug product label described below. The nonclinical information contained in the Efudex cream label is incorporated into the appropriate sections of the 4% 5-fluorouracil cream label. In addition, clinical information related to the reproductive toxicology of 5-fluorouracil that was incorporated into the Efudex cream label has been incorporated into the 4% 5-fluorouracil cream label. The wording contained in section 12.1 that is highlighted and in italics text is a general recommendation for the label.

4 CONTRAINDICATIONS

4.1 Pregnancy

(b) (4)

5 WARNINGS AND PRECAUTIONS

(b) (4)

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY

Teratogenic Effects: Pregnancy Category X. (b) (4) [see *Contraindications* (4.1)].

(b) (4)

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil. Studies with (b) (4) the active ingredient of TRADENAME, (b) (4) fluorouracil, (b) (4) have shown mutagenic effects in in vitro and in vivo tests (b) (4) and impairment of fertility in in vivo animal studies (b) (4).

(b) (4) fluorouracil was positive (b) (4) n three *in vitro* cell neoplastic transformation assays (b) (4) In the C3H/10T½ clone 8 mouse embryo cell system, the resulting (b) (4) -morphologically transformed cells (b) (4) formed tumors when inoculated into immunosuppressed syngeneic mice. (b) (4)

Although no evidence for mutagenic activity of fluorouracil was observed in 3 studies utilizing the Ames test, mutagenic activity was observed in the survival count rec-assay with *Bacillus subtilis* and in the *Drosophila* wing-hair spot test. Fluorouracil (b) (4) produced petite mutations in *Saccharomyces cerevisiae* and demonstrated positive results in the micronucleus test using bone marrow cells of male mice.

Fluorouracil demonstrated clastogenic activity *in vitro* in Chinese hamster fibroblasts at concentrations of 1.0 and 2.0 µg/mL and was associated with chromatid gaps, breaks, and exchanges. In human lymphocytes, fluorouracil increased sister chromatid exchange *in vitro*. Additionally, an increase in numerical and structural chromosome aberrations has been observed in peripheral lymphocytes of patients treated with 5-fluorouracil.

In rats, chromosomal abnormalities and changes in chromosome organization in spermatogonia have been observed after intraperitoneal administration of 125 to 250 mg/kg of fluorouracil. Spermatogonial differentiation was also inhibited and resulted in transient infertility. Fluorouracil was inactive, however, at oral doses of 5 to 80 mg/kg/day in studies with a strain of mouse which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens. In female rats, fluorouracil administered intraperitoneally at doses of 25 and 50 mg/kg during the preovulatory phase of oogenesis resulted in a significant reduction in the incidence of fertile matings, a delay in the development of preimplantation and postimplantation embryos, an increased incidence of preimplantation lethality, and an induction of chromosomal anomalies in these embryos. In mice, single intravenous or intraperitoneal injections of 5-fluorouracil were toxic to differentiated spermatogonia and spermatocytes (at 500 mg/kg) and produced abnormalities in spermatids (at 50 mg/kg).

(b) (4)

(b) (4)

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

cc:
DDDP/DIV DIR/WALKER
DDDP/PHARM SUP/BROWN
DDDP/PHARM/HILL
DDDP/MO/KETTL
DDDP/PM/CARR

APPENDIX/ATTACHMENTS

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

/s/

Barbara Hill
3/25/2008 07:53:28 AM
PHARMACOLOGIST

Paul Brown
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