FERNDALE LABORATORIES INC

June 28, 2001

Rec'd 6/29/01

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: ANDA Suitability Petition for Fluorouracil Topical Solution USP, 2.5%

Dear Sir or Madam:

The undersigned respectfully submits this citizen petition pursuant to 21 U.S.C. § 355(j)(2)(C) and 21 CFR §§10.30 and 314.93, to request that the Commissioner of Food and Drugs make a determination of ANDA suitability for a 2.5% topical preparation of a dermatological drug product, Fluorouracil Topical Solution USP, containing the fluorinated pyrimidine, 5-fluorouracil, an antineoplastic antimetabolite, where the reference listed drug is a 2% topical solution. The health care community would benefit from the alternative choice provided by the availability of a 2.5% topical solution, which is pharmaceutically elegant, and cosmetically acceptable to the end-user. The proposed 2.5% strength would give physicians greater flexibility in prescribing than is available in the current strengths of 0.5%, 1%, 2%, and 5%.

Action Requested

Petitioner requests that the Commissioner of Food and Drugs make a determination that an abbreviated new drug application (ANDA) is suitable for a topical solution containing 2.5% 5-fluorouracil.

Statement Of Grounds

The Drug Price Competition and Patent Term Restoration Act of 1984 ("The Hatch - Waxman Act") extends eligibility for the submission of ANDAs to certain drug products identical to those approved via new drug applications, as identified in the Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") issued by the

01P0288

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Food and Drug Administration. Where the proposed drug product differs from the "reference listed drug" in one or more respects, a person may petition the Agency, under section 505(j)(2)(c) of the Act, for a determination of ANDA suitability as a similar or related drug product.

The reference listed drug product, which forms the basis for this petition, is a topical solution containing 2% of the active pharmaceutical ingredient, 5-fluorouracil (Efudex® 2% Solution – NDA 16-831 – manufactured for ICN Pharmaceuticals Inc., by Hoffman-La Roche Inc.) Exhibit A contains page 3-162 from the 20th edition of the "Orange Book", showing the Reference Listed Drug designation as determined by the FDA.

In the petitioner's opinion and to the best of petitioner's knowledge, there are no applicable U.S. patents with respect to the drug substance, 5-fluorouracil, and the drug product, Efudex®, have expired or which claim a use for the drug substance or drug product referenced to in this petition. The relevant page, ADA-24, from the 20th edition of the *Orange Book* is enclosed as Exhibit B.

The proposed drug product, Fluorouracil Topical Solution USP, 2.5%, differs from the reference listed drug product, Efudex® 2% Solution, only in regard to strength (a 2.5% solution as apposed to a 2% solution). It is identical with respect to active ingredient, dosage form, route of administration and conditions of use. Pursuant to 21 CFR §314.93(d), labeling for the reference listed drug is included in Exhibit D.

Other approved topical dosage forms and strengths of 5-fluorouracil are available (see also Exhibit A). These include:

Product	**Strength**	**Dosage Form**	**A/NDA No**
Efudex® (ICN)	5%	Topical Solution	16-831
Fluoroplex® (Allergan Herbert)	1%	Topical Solution	16-765
Efudex® (ICN)	5%	Topical Cream	16-831
Fluoroplex® (Allergan Herbert)	1%	Topical Cream	16-988
Carac™ (Dermik)	0.5%	Topical Cream	20-985

The health care community would benefit from the alternative choice provided by the availability of a 2.5% topical solution, which is pharmaceutically elegant, and cosmetically acceptable to the end-user. The proposed 2.5% strength would give physicians greater flexibility in prescribing than is available in the current strengths of 0.5%, 1%, 2%, and 5%.

The proposed drug product contains the same active ingredient, in the same dosage form and route of administration, and would be labeled with the same conditions for use as the reference listed drug, Efudex® 2% Solution.

Draft labeling (insert) for the proposed drug product, which is modeled on the reference listed drug, is enclosed in Exhibit E. Side by Side insert comparison is enclosed in Exhibit C.

The finished product will be packaged in a container/closure system that is appropriate to, and compatible with the dosage form.

Based on the above, Petitioner believes that Fluorouracil Topical Solution USP, 2.5% warrants a finding of ANDA suitability, and that the Commissioner should grant permission for the filing of an ANDA for Fluorouracil Topical Solution USP, 2.5%.

Environmental Impact

Petitioner hereby claims a categorical exclusion from the requirement of an Environmental Assessment (EA) statement. The approval of this petition will result in an abbreviated new drug application (ANDA) for a drug product that will be excluded from the requirement of an Environmental Assessment statement, pursuant to 21 CFR §25.31(a).

Economic Impact

In accordance with 21 CFR §10.30(b), information on economic impact will be submitted only when requested by the Commissioner following review of this petition.

Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes

representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

Deborah L. Theres
Manager, Regulatory Affairs
Ferndale Laboratories, Inc.

Enclosures:

Exhibit A	Approved Drug Products with Therapeutic Equivalence Evaluations, 20th edition, p. 3-162
Exhibit B	Approved Drug Products with Therapeutic Equivalence Evaluations, 20th edition, p. ADA24
Exhibit C	Side by Side Insert Comparison
Exhibit D	Labeling for the Reference Listed Drug (Efudex®)
Exhibit E	Draft labeling for the proposed drug product

Exhibit A

FLUOROMETHOLONE

OINTMENT; OPHTHALMIC

	FML			
	+ ALLERGAN	0.1%	N17760 001	SEP 04, 1985

SUSPENSION/DROPS; OPHTHALMIC

	FLUOR-OP			
AB	CIBA	**0.1%**	**N70185 001**	FEB 27, 1986
	FML			
AB	+ ALLERGAN	**0.1%**	**N16851 002**	JUL 28, 1982
	FML FORTE			
	ALLERGAN	0.25%	N19216 001	APR 23, 1986

FLUOROMETHOLONE; SULFACETAMIDE SODIUM

SUSPENSION/DROPS; OPHTHALMIC

	FML-S			
	+ ALLERGAN	0.1%;10%	N19525 001	SEP 29, 1989

FLUOROMETHOLONE ACETATE

SUSPENSION/DROPS; OPHTHALMIC

	FLAREX			
	+ ALCON	0.1%	N19079 001	FEB 11, 1986

FLUOROMETHOLONE ACETATE; TOBRAMYCIN

SUSPENSION/DROPS; OPHTHALMIC

	TOBRASONE			
	+ ALCON	0.1%;0.3%	N50628 001	JUL 21, 1989

FLUOROURACIL

CREAM; TOPICAL

	EFUDEX			
	+ ICN	5%	N16831 003	
	FLUOROPLEX			
	+ ALLERGAN HERBERT	1%	N16988 001	

FLUOROURACIL

CREAM; TOPICAL

	FLUOROURACIL			
	+ DERMIK LABS	0.5%	N20985 001	OCT 27, 2000

INJECTABLE; INJECTION

	ADRUCIL			
AP	PHARMACIA AND UPJOHN	**50MG/ML**	**N40023 001**	OCT 18, 1991
AP	+	**50MG/ML**	**N81225 001**	AUG 28, 1991
	FLUOROURACIL			
AP	AM PHARM PARTNERS	**50MG/ML**	**N40278 001**	SEP 30, 1998
AP		**50MG/ML**	**N40279 001**	SEP 30, 1998
AP	BEDFORD	**50MG/ML**	**N89508 001**	JAN 26, 1988
AP	BIGMAR	**50MG/ML**	**N40291 001**	MAR 24, 1999
AP		**50MG/ML**	**N40379 001**	NOV 15, 2000
AP	GENSIA SICOR PHARMS	**50MG/ML**	**N40333 001**	JAN 27, 2000
AP		**50MG/ML**	**N40334 001**	FEB 25, 2000
AP	+ ICN PUERTO RICO	**50MG/ML**	**N12209 001**	
AP	STERIS	**50MG/ML**	**N87792 001**	OCT 13, 1982

SOLUTION; TOPICAL

	EFUDEX			
	+ ICN	2%	N16831 001	
	+	5%	N16831 002	
	FLUOROPLEX			
	+ ALLERGAN HERBERT	1%	N16765 001	

FLUOXETINE HYDROCHLORIDE

CAPSULE; ORAL

	PROZAC			
	LILLY	EQ 10MG BASE	N18936 006	DEC 23, 1992
		EQ 20MG BASE	N18936 001	DEC 29, 1987

Exhibit B

PRESCRIPTION AND OTC DRUG PRODUCT
PATENT AND EXCLUSIVITY DATA

APPL/PROD NUMBER	INGREDIENT NAME; TRADE NAME	PATENT NUMBER	PATENT EXPIRES	USE CODE	EXCLUS CODE	EXCLUS EXPIRES
020409 001	FLUNISOLIDE;NASAREL	4782047	MAY 22, 2006			
		4983595	MAY 22, 2006			
		4933168	JUN 12, 2007			
019452 001	FLUOCINOLONE ACETONIDE;DERMA-SMOOTHE/FS				I-265	AUG 18, 2002
020985 001	FLUOROURACIL;FLUOROURACIL				NP	OCT 27, 2003
018936 001	FLUOXETINE HYDROCHLORIDE;PROZAC	4626549	DEC 02, 2003	U-154		
		4314081	FEB 02, 2001			
		4626549	DEC 02, 2003	U-84		
		4314081*PED	AUG 02, 2001			
		4626549*PED	JUN 02, 2004	U-154		
		4626549*PED	JUN 02, 2004	U-84		
018936 003	FLUOXETINE HYDROCHLORIDE;PROZAC	4314081	FEB 02, 2001			
		4626549	DEC 02, 2003	U-154		
		4626549	DEC 02, 2003	U-84		
		4314081*PED	AUG 02, 2001			
		4626549*PED	JUN 02, 2004	U-154		
		4626549*PED	JUN 02, 2004	U-84		
018936 004	FLUOXETINE HYDROCHLORIDE;PROZAC	4314081	FEB 02, 2001			
		4314081*PED	AUG 02, 2001			
		4626549	DEC 02, 2003	U-154		
		4626549	DEC 02, 2003	U-84		
		4626549*PED	JUN 02, 2004	U-154		
		4626549*PED	JUN 02, 2004	U-84		
018936 006	FLUOXETINE HYDROCHLORIDE;PROZAC	4314081	FEB 02, 2001			
		4626549	DEC 02, 2003	U-154		
		4626549	DEC 02, 2003	U-84		
		4314081*PED	AUG 02, 2001			
		4626549*PED	JUN 02, 2004	U-154		
		4626549*PED	JUN 02, 2004	U-84		
020101 001	FLUOXETINE HYDROCHLORIDE;PROZAC	4314081	FEB 02, 2001			
		4626549	DEC 02, 2003	U-84		
		4626549	DEC 02, 2003	U-154		
		4314081*PED	AUG 02, 2001			
		4626549*PED	JUN 02, 2004	U-84		
		4626549*PED	JUN 02, 2004	U-154		
020974 001	FLUOXETINE HYDROCHLORIDE;PROZAC	4626549	DEC 02, 2003	U-84		
		4626549	DEC 02, 2003	U-154		
		4314081	FEB 02, 2001			
		4314081*PED	AUG 02, 2001			
		4626549*PED	JUN 02, 2004	U-84		
		4626549*PED	JUN 02, 2004	U-154		
020974 002	FLUOXETINE HYDROCHLORIDE;PROZAC	4626549	DEC 02, 2003	U-84		
		4626549	DEC 02, 2003	U-154		
		4314081	FEB 02, 2001			
		4314081*PED	AUG 02, 2001			
		4626549*PED	JUN 02, 2004	U-84		
		4626549*PED	JUN 02, 2004	U-154		

Exhibit C

Reference Listed Drug | **Proposed Drug**

Changes to Insert
- removed references to EFUDEX
- removed references to cream
- removed references to 5% strength
- changed strength to 2.5%
- changed inactive ingredients to conform to Ferndale formulation
- deleted references to Superficial Basal Cell Carcinoma since this indication is for 5% strength
- revised how supplied section
- changed manufacturer/supplier information to reflect Ferndale Laboratories, Inc.

EFUDEX®

[*ef 'u-dex*]
brand of fluorouracil
TOPICAL SOLUTIONS AND CREAM

For Topical Dermatological Use Only – Not for Ophthalmic Use

DESCRIPTION

Efudex Solutions and Cream are topical preparations containing the fluorinated pyrimidine 5-fluorouracil, an antineoplastic antimetabolite.

Efudex Solution consists of 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris(hydroxymethyl)aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Efudex Cream contains 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

Chemically, fluorouracil is 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione. It is a white to practically white, crystalline powder which is sparingly soluble in water and

Fluorouracil

TOPICAL SOLUTION USP, 2.5%

For Topical Dermatological Use Only – Not for Ophthalmic Use

DESCRIPTION

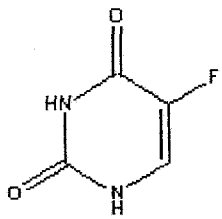
Fluorouracil Topical Solution USP, 2.5% is a topical preparation containing the fluorinated pyrimidine 5-fluorouracil, an antineoplastic antimetabolite.

Fluorouracil Topical Solution USP consists of 2.5% fluorouracil on a weight/weight basis, compounded with arginine, polyethylene glycol, propylene glycol, lactic acid and sodiurm hydroxide.

Chemically, fluorouracil is 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione. It is a white to practically white, crystalline powder which is sparingly soluble in water and

Reference Listed Drug

slightly soluble in alcohol. One gram of fluorouracil is soluble in 100 mL of propylene glycol. The molecular weight of 5-fluorouracil is 130.08 and the structural formula is:



CLINICAL PHARMACOLOGY

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 which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and take up fluorouracil at a more rapid rate. The catabolic metabolism of fluorouracil results in degradation products (eg, CO_2, urea, α-fluoro-β-alanine) which are inactive.

Systemic absorption studies of topically applied fluorouracil have been performed on patients with actinic keratoses using tracer amounts of ^{14}C-labeled fluorouracil added to a 5% preparation. All patients had been receiving nonlabeled fluorouracil until the peak of the inflammatory reaction occurred (2 to 3 weeks), ensuring that the time of maximum absorption was used for

Proposed Drug

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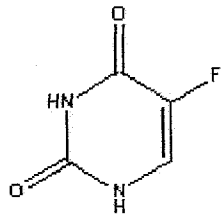

CLINICAL PHARMACOLOGY

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Reference Listed Drug	Proposed Drug
measurement. One gram of labeled preparation was applied to the entire face and neck and left in place for 12 hours. Urine samples were collected. At the end of 3 days, the total recovery ranged between 0.48% and 0.94% with an average of 0.76%, indicating that approximately 5.98% of the topical dose was absorbed systematically. If applied twice daily, this would indicate systemic absorption of topical fluorouracil to be in the range of 5 to 6 mg per daily dose of 100 mg. In an additional study, negligible amounts of labeled material were found in plasma, urine and expired CO_2 after 3 days of treatment with topically applied ^{14}C-labeled fluorouracil.	measurement. One gram of labeled preparation was applied to the entire face and neck and left in place for 12 hours. Urine samples were collected. At the end of 3 days, the total recovery ranged between 0.48% and 0.94% with an average of 0.76%, indicating that approximately 5.98% of the topical dose was absorbed systematically. If applied twice daily, this would indicate systemic absorption of topical fluorouracil to be in the range of 5 to 6 mg per daily dose of 100 mg. In an additional study, negligible amounts of labeled material were found in plasma, urine and expired CO_2 after 3 days of treatment with topically applied ^{14}C-labeled fluorouracil.
INDICATIONS AND USAGE Efudex is recommended for the topical treatment of actinic or solar keratoses. In the 5% strength it is also useful in the treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites. Safety and efficacy in other indications have not been established. The diagnosis should be established prior to treatment, since this method has not been proven effective in other types of basal cell carcinomas. With isolated, easily accessible basal cell carcinomas, surgery is preferred since success with such lesions is almost 100%. The success rate with Efudex Cream and Solution is approximately 93%, based on 113 lesions in 54 patients. Twenty-five lesions treated with the solution produced 1 failure and 88 lesions treated with the cream produced 7 failures.	**INDICATIONS AND USAGE** Fluorouracil Topical Solution USP is recommended for the topical treatment of actinic or solar keratoses.

Reference Listed Drug

CONTRAINDICATIONS

Efudex may cause fetal harm when administered to a pregnant woman.

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.

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 (see CLINICAL PHARMACOLOGY).

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

Proposed Drug

CONTRAINDICATIONS

Fluorouracil Topical Solution USP may cause fetal harm when administered to a pregnant woman.

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 Fluorouracil Topical Solution USP as recommended. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when Fluorouracil Topical Solution USP was applied to mucous membrane areas. Multiple birth defects have been reported in a fetus of a patient treated with intravenous fluorouracil.

Animal reproduction studies have not been conducted with Fluorouracil Topical Solution USP. 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 (see CLINICAL PHARMACOLOGY).

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Reference Listed Drug	Proposed Drug
mg/kg resulted in abortion.	mg/kg resulted in abortion.
Efudex is contraindicated in women who are or may become pregnant during therapy. If this drug is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be appraised of the potential hazard to the fetus.	**Fluorouracil Topical Solution USP is contraindicated in women who are or may become pregnant during therapy. If this drug is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be appraised of the potential hazard to the fetus.**
Efudex is also contraindicated in patients with known hypersensitivity to any of its components.	**Fluorouracil Topical Solution USP is also contraindicated in patients with known hypersensitivity to any of its components.**
WARNINGS: Application to mucous membranes should be avoided due to the possibility of local inflammation and ulceration. Additionally, cases of miscarriage and a birth detect (ventricular septal defect) have been reported when Efudex was applied to mucous membrane areas during pregnancy.	**WARNINGS: Application to mucous membranes should be avoided due to the possibility of local inflammation and ulceration. Additionally, cases of miscarriage and a birth detect (ventricular septal defect) have been reported when Fluorouracil Topical Solution USP was applied to mucous membrane areas during pregnancy.**
Occlusion of the skin with resultant hydration has been shown to increase precutaneous penetration of several topical preparations. If any occlusive dressing is used in treatment of basal cell carcinoma, there may be an increase in the severity of inflammatory reactions in the adjacent normal skin. A porous gauze dressing may be applied for cosmetic reasons without increase in reaction.	Occlusion of the skin with resultant hydration has been shown to increase precutaneous penetration of several topical preparations. If any occlusive dressing is used, there may be an increase in the severity of inflammatory reactions in the adjacent normal skin. A porous gauze dressing may be applied for cosmetic reasons without increase in reaction.
Exposure to ultraviolet rays should he minimized during and immediately following treatment with Efudex because the intensity of the reaction may be increased.	Exposure to ultraviolet rays should he minimized during and immediately following treatment with Fluorouracil Topical Solution USP because the intensity of the reaction may be increased.

Reference Listed Drug	Proposed Drug
PRECAUTIONS *General:* There is a possibility of increased absorption through ulcerated or inflamed skin. *Information for Patients:* Patients should be forewarned that the reaction in the treated areas may be unsightly during therapy and, usually, for several weeks following cessation of therapy. Patients should be instructed to avoid exposure to ultraviolet rays during and immediately following treatment with Efudex because the intensity of the reaction may be increased. If Efudex is applied with the fingers, the hands should be washed immediately afterwards. Efudex should not be applied on the eyelids or directly into the eyes, nose or mouth because irritation may occur. *Laboratory Tests:* Solar keratoses which do not respond should be biopsied to confirm the diagnosis. Follow-up biopsies should be performed as indicated in the management of superficial basal cell carcinoma. *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 Efudex, 5-fluorouracil, have shown positive effects in in vitro tests for mutagenicity and on impairment of fertility. 5-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 immunosurpressed syngeneic mice. While no evidence for mutagenic activity	**PRECAUTIONS** *General:* There is a possibility of increased absorption through ulcerated or inflamed skin. *Information for Patients:* Patients should be forewarned that the reaction in the treated areas may be unsightly during therapy and, usually, for several weeks following cessation of therapy. Patients should be instructed to avoid exposure to ultraviolet rays during and immediately following treatment with Fluorouracil Topical Solution USP because the intensity of the reaction may be increased. If Fluorouracil Topical Solution USP is applied with the fingers, the hands should be washed immediately afterwards. Fluorouracil Topical Solution USP should not be applied on the eyelids or directly into the eyes, nose or mouth because irritation may occur. *Laboratory Tests:* Solar keratoses which do not respond should be biopsied to confirm the diagnosis. *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 Fluorouracil Topical Solution USP, 5-fluorouracil, have shown positive effects in in vitro tests for mutagenicity and on impairment of fertility. 5-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 immunosurpressed syngeneic mice. While no evidence for mutagenic activity

Reference Listed Drug	Proposed Drug
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 with this product. 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	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 with this product. 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

Reference Listed Drug

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.
Pregnancy: Pregnancy: **Teratogenic Effects: Pregnancy Category X:** See CONTRAINDICATIONS section.
Nursing Mothers: It is not known whether Efudex is excreted in human milk. Because there is some systemic absorption of fluorouracil after topical administration (see CLINICAL PHARMACOLOGY), because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue use of the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
The most frequent adverse reactions to Efudex occur locally and are often related to an extension of the pharmacological activity of the drug. These 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 (ventrictular septal defect) have been reported when Efudex was applied to mucous membrane areas. Leukocytosis is the most frequent hematological side effect.

Proposed Drug

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.
Pregnancy: Pregnancy: **Teratogenic Effects: Pregnancy Category X:** See CONTRAINDICATIONS section.
Nursing Mothers: It is not known whether Fluorouracil Topical Solution USP is excreted in human milk. Because there is some systemic absorption of fluorouracil after topical administration (see CLINICAL PHARMACOLOGY), because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue use of the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
The most frequent adverse reactions to Fluorouracil Topical Solution USP occur locally and are often related to an extension of the pharmacological activity of the drug. These 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 (ventrictular septal defect) have been reported when Fluorouracil Topical Solution USP was applied to mucous membrane areas. Leukocytosis is the most frequent hematological side effect.

Reference Listed Drug	Proposed Drug
Although a causal relationship is remote, other adverse reactions which have been reported infrequently are: *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.	Although a causal relationship is remote, other adverse reactions which have been reported infrequently are: *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.
OVERDOSAGE There have been no reports of overdosage with Efudex. The oral LD_{50} for the 5% topical cream was 234 mg/kg in rats and 39 mg/kg in dogs. These doses represented 11.7 and 1.95 mg/kg of fluorouracil, respectively. Studies with a 5% topical solution yielded an oral LD_{50} of 214 mg/kg in rats and 28.5 in dogs, corresponding to 10.7 and 14.3 mg/kg of fluorouracil, respectively. The topical application of the 5% cream to rats yielded an LD_{50} of greater than 500 mg/kg.	**OVERDOSAGE** There have been no reports of overdosage with Fluorouracil Topical Solution USP. The oral LD_{50} for a 5% topical cream was 234 mg/kg in rats and 39 mg/kg in dogs. These doses represented 11.7 and 1.95 mg/kg of fluorouracil, respectively. Studies with a 5% topical solution yielded an oral LD_{50} of 214 mg/kg in rats and 28.5 in dogs, corresponding to 10.7 and 14.3 mg/kg of fluorouracil, respectively. The topical application of a 5% cream to rats yielded an LD_{50} of greater than 500 mg/kg.
DOSAGE AND ADMINISTRATION When Efudex is applied to a lesion, a response occurs with the following sequence; erythema, usually followed by vesiculation, desquamation, erosion and reepithelialization. Efudex should be applied preferably with a nonmetal applicator or suitable glove. If Efudex is applied with the fingers, the	**DOSAGE AND ADMINISTRATION** When Fluorouracil Topical Solution USP is applied to a lesion, a response occurs with the following sequence; erythema, usually followed by vesiculation, desquamation, erosion and reepithelialization. Fluorouracil Topical Solution USP should be applied preferably with a nonmetal applicator or suitable glove. If Fluorouracil

Reference Listed Drug	Proposed Drug
hands should be washed immediately afterward.	Topical Solution USP is applied with the fingers, the hands should be washed immediately afterward.
Actinic or Solar Keratosis: Apply cream or solution twice daily in an amount sufficient to cover the lesions. Medication should be continued until the inflammatory response reaches the erosion state, at which time use of the drug should be terminated. The usual duration of therapy is from 2 to 4 weeks. Complete healing of the lesions may not be evident for 1 to 2 months following cessation of Efudex therapy.	*Actinic or Solar Keratosis:* Apply Fluorouracil Topical Solution USP twice daily in an amount sufficient to cover the lesions. Medication should be continued until the inflammatory response reaches the erosion state, at which time use of the drug should be terminated. The usual duration of therapy is from 2 to 4 weeks. Complete healing of the lesions may not be evident for 1 to 2 months following cessation of Fluorouracil Topical Solution USP therapy.
Superficial Basal Cell Carcinomas: **Only the 5% strength is recommended.** Apply cream or solution twice daily in an amount sufficient to cover the lesions. Treatment should be continued for at least 3 to 6 weeks. Therapy may be required for as long as 10 to 12 weeks before the lesions are obliterated. As in any neoplastic condition, the patient should be followed for a reasonable period of time to determine if a cure has been obtained.	
HOW SUPPLIED Efudex Solution is available in 10 mL drop dispensers containing either 2% (NDC 0187-3202-10) or 5% (NDC 0187-3203-10) fluorouracil on a weight/weight basis compounded with propylene glycol, tris(hydroxymethyl)aminomethane, hyroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate. Efudex Cream is available in 25-gm tubes containing 5% fluorouracil (NDC 0187-3204-26) in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).	**HOW SUPPLIED** Fluorouracil Topical Solution USP is available in 10 mL drop dispensers containing 2.5% fluorouracil on a weight/weight basis, compounded with arginine, polyethylene glycol, propylene glycol, lactic acid and sodiurm hydroxide.

Reference Listed Drug	Proposed Drug
Store at 25°C (77°F); excursion permitted to 15°C - 30°C (59°F - 86°F).	Store at 25°C (77°F); excursion permitted to 15°C - 30°C (59°F - 86°F).
Manufactured for ICN Pharmaceuticals Inc. Costa Mesa, CA 92626 by Hoffman-La Roche Inc. Nutley, N.J. 07110 ICN Pharmaceuticals, Inc. ICN Plaza 3300 Hyland Avenue Costa Mesa, California 92626 714-545-0100	Manufactured by Ferndale Laboratories, Inc. Ferndale, MI 48220
Revised: February 1998	Revised: 06/01

Exhibit D

Retyped from Physician's Desk Reference 1999

EFUDEX®

[*ef 'u-dex*]
brand of fluorouracil
TOPICAL SOLUTIONS AND CREAM

For Topical Dermatological Use Only –
Not for Ophthalmic Use

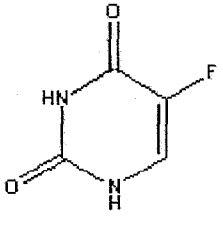
DESCRIPTION

Efudex Solutions and Cream are topical preparations containing the fluorinated pyrimidine 5-fluorouracil, an antineoplastic antimetabolite.

Efudex Solution consists of 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris(hydroxymethyl)aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Efudex Cream contains 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

Chemically, fluorouracil is 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione. It is a white to practically white, crystalline powder which is sparingly soluble in water and slightly soluble in alcohol. One gram of fluorouracil is soluble in 100 mL of propylene glycol. The molecular weight of 5-fluorouracil is 130.08 and the structural formula is:



CLINICAL PHARMACOLOGY

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 which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and take up fluorouracil at a more rapid rate. The catabolic metabolism of fluorouracil results in degradation products (eg, CO_2, urea, α-fluoro-β-alanine) which are inactive.

Systemic absorption studies of topically applied fluorouracil have been performed on patients with actinic keratoses using tracer amounts of ^{14}C-labeled fluorouracil added to a 5% preparation. All patients had been receiving nonlabeled fluorouracil until the peak of the

inflammatory reaction occurred (2 to 3 weeks), ensuring that the time of maximum absorption was used for measurement. One gram of labeled preparation was applied to the entire face and neck and left in place for 12 hours. Urine samples were collected. At the end of 3 days, the total recovery ranged between 0.48% and 0.94% with an average of 0.76%, indicating that approximately 5.98% of the topical dose was absorbed systematically. If applied twice daily, this would indicate systemic absorption of topical fluorouracil to be in the range of 5 to 6 mg per daily dose of 100 mg. In an additional study, negligible amounts of labeled material were found in plasma, urine and expired CO_2 after 3 days of treatment with topically applied ^{14}C-labeled fluorouracil.

INDICATIONS AND USAGE

Efudex is recommended for the topical treatment of actinic or solar keratoses. In the 5% strength it is also useful in the treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites. Safety and efficacy in other indications have not been established.

The diagnosis should be established prior to treatment, since this method has not been proven effective in other types of basal cell carcinomas. With isolated, easily accessible basal cell carcinomas, surgery is preferred since success with such lesions is almost 100%. The success rate with Efudex Cream and Solution is approximately 93%, based on 113 lesions in 54 patients. Twenty-five lesions treated with the solution produced 1 failure and 88 lesions treated with the cream produced 7 failures.

CONTRAINDICATIONS

Efudex may cause fetal harm when administered to a pregnant woman.

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.

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 (see CLINICAL PHARMACOLOGY). 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.

Efudex is contraindicated in women who are or may become pregnant during therapy. If this drug is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be appraised of the potential hazard to the fetus.

Efudex is also contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS: Application to mucous membranes should be avoided due to the possibility of local inflammation and ulceration. Additionally, cases of miscarriage and a birth detect (ventricular septal defect) have been reported when Efudex was applied to mucous membrane areas during pregnancy.

Occlusion of the skin with resultant hydration has been shown to increase precutaneous penetration of several topical preparations. If any occlusive dressing is used in treatment of basal cell carcinoma, there may be an increase in the severity of inflammatory reactions in the adjacent normal skin. A porous gauze dressing may be applied for cosmetic reasons without increase in reaction.

Exposure to ultraviolet rays should he minimized during and immediately following treatment with Efudex because the intensity of the reaction may be increased.

PRECAUTIONS

General: There is a possibility of increased absorption through ulcerated or inflamed skin.

Information for Patients: Patients should be forewarned that the reaction in the treated areas may be unsightly during therapy and, usually, for several weeks following cessation of therapy. Patients should be instructed to avoid exposure to ultraviolet rays during and immediately following treatment with Efudex because the intensity of the reaction may be increased. If Efudex is applied with the fingers, the hands should be washed immediately afterwards. Efudex should not be applied on the eyelids or directly into the eyes, nose or mouth because irritation may occur.

Laboratory Tests: Solar keratoses which do not respond should be biopsied to confirm the diagnosis. Follow-up biopsies should be performed as indicated in the management of superficial basal cell carcinoma.

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 Efudex, 5-fluorouracil, have shown positive effects in in vitro tests for mutagenicity and on impairment of fertility.

5-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 immunosurpressed 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 with this product.

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.

Pregnancy: Pregnancy: **Teratogenic Effects: Pregnancy Category X:** See CONTRAINDICATIONS section.

Nursing Mothers: It is not known whether Efudex is excreted in human milk. Because there is some systemic absorption of fluorouracil after topical administration (see CLINICAL PHARMACOLOGY), because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue use of the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The most frequent adverse reactions to Efudex occur locally and are often related to an extension of the pharmacological activity of the drug. These 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 (ventrictular septal defect) have been reported when Efudex was applied to mucous membrane areas. Leukocytosis is the most frequent hematological side effect.

Although a causal relationship is remote, other adverse reactions which have been reported infrequently are:

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.

OVERDOSAGE

There have been no reports of overdosage with Efudex.

The oral LD_{50} for the 5% topical cream was 234 mg/kg in rats and 39 mg/kg in dogs. These doses represented 11.7 and 1.95 mg/kg of fluorouracil, respectively. Studies with a 5% topical solution yielded an oral LD_{50} of 214 mg/kg in rats and 28.5 in dogs, corresponding to 10.7 and

14.3 mg/kg of fluorouracil, respectively. The topical application of the 5% cream to rats yielded an LD_{50} of greater than 500 mg/kg.

DOSAGE AND ADMINISTRATION

When Efudex is applied to a lesion, a response occurs with the following sequence; erythema, usually followed by vesiculation, desquamation, erosion and reepithelialization.

Efudex should be applied preferably with a nonmetal applicator or suitable glove. If Efudex is applied with the fingers, the hands should be washed immediately afterward.

Actinic or Solar Keratosis: Apply cream or solution twice daily in an amount sufficient to cover the lesions. Medication should be continued until the inflammatory response reaches the erosion state, at which time use of the drug should be terminated. The usual duration of therapy is from 2 to 4 weeks. Complete healing of the lesions may not be evident for 1 to 2 months following cessation of Efudex therapy.

Superficial Basal Cell Carcinomas: **Only the 5% strength is recommended.** Apply cream or solution twice daily in an amount sufficient to cover the lesions. Treatment should be continued for at least 3 to 6 weeks. Therapy may be required for as long as 10 to 12 weeks before the lesions are obliterated. As in any neoplastic condition, the patient should be followed for a reasonable period of time to determine if a cure has been obtained.

HOW SUPPLIED

Efudex Solution is available in 10 mL drop dispensers containing either 2% (NDC 0187-3202-10) or 5% (NDC 0187-3203-10) fluorouracil on a weight/weight basis compounded with propylene glycol, tris(hydroxymethyl)aminomethane, hyroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Efudex Cream is available in 25-gm tubes containing 5% fluorouracil (NDC 0187-3204-26) in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

Store at 25°C (77°F); excursion permitted to 15°C - 30°C (59°F - 86°F).

Manufactured for ICN Pharmaceuticals Inc.
Costa Mesa, CA 92626
by Hoffman-La Roche Inc.
Nutley, N.J. 07110
ICN Pharmaceuticals, Inc.
ICN Plaza
3300 Hyland Avenue
Costa Mesa, California 92626
714-545-0100

Revised: February 1998

Exhibit E

Changes to Insert

- removed references to EFUDEX
- removed references to cream
- removed references to 5% strength
- changed strength to 2.5%
- changed inactive ingredients to conform to Ferndale formulation
- deleted references to Superficial Basal Cell Carcinoma since this indication is for 5% strength
- revised how supplied section
- changed manufacturer/supplier information to reflect Ferndale Laboratories, Inc.

FLUOROURACIL
TOPICAL SOLUTION USP, 2.5%

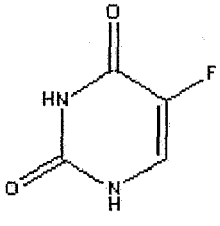
For Topical Dermatological Use Only–
Not for Ophthalmic Use

DESCRIPTION

Fluorouracil Topical Solution, USP is a topical preparation containing the fluorinated pyrimidine 5-fluorouracil, an antineoplastic antimetabolite.

Fluorouracil Topical Solution USP consists of 2.5% fluorouracil on a weight/weight basis, compounded with polyethylene glycol, 400, NF, propylene glycol USP, lactic acid USP, sodium hydroxide NF.

Chemically, fluorouracil is 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione. It is a white to practically white, crystalline powder which is sparingly soluble in water and slightly soluble in alcohol. One gram of fluorouracil is soluble in 100 mL of propylene glycol. The molecular weight of 5-fluorouracil is 130.08 and the structural formula is:



CLINICAL PHARMACOLOGY

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 which provokes

unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and take up fluorouracil at a more rapid rate. The catabolic metabolism of fluorouracil results in degradation products (e.g., CO_2, urea, -fluoro-alanine) which are inactive.

Systemic absorption studies of topically applied fluorouracil have been performed on patients with actinic keratoses using tracer amounts of ^{14}C-labeled fluorouracil added to a 5% preparation. All patients had been receiving nonlabeled fluorouracil until the peak of the inflammatory reaction occurred (2 to 3 weeks), ensuring that the time of maximum absorption was used for measurement. One gram of labeled preparation was applied to the entire face and neck and left in place for 12 hours. Urine samples were collected. At the end of 3 days, the total recovery ranged between 0.48% and 0.94% with an average of 0.76%, indicating that approximately 5.98% of the topical dose was absorbed systematically. If applied twice daily, this would indicate systemic absorption of topical fluorouracil to be in the range of 5 to 6 mg per daily dose of 100 mg. In an additional study, negligible amounts of labeled material were found in plasma, urine and expired CO_2 after 3 days of treatment with topically applied ^{14}C-labeled fluorouracil.

INDICATIONS AND USAGE

Fluorouracil Topical Solution USP is recommended for the topical treatment of actinic or solar keratoses.

CONTRAINDICATIONS

Fluorouracil Topical Solution USP may cause fetal harm when administered to a pregnant woman.

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 fluorouracil as recommended. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when fluorouracil was applied to mucous membrane areas. Multiple birth defects have been reported in a fetus of a patient treated with intravenous fluorouracil.

Animal reproduction studies have not been conducted with fluorouracil. 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 (see **CLINICAL PHARMACOLOGY**). 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. Doses higher than 40 mg/kg resulted in abortion.

Fluorouracil Topical Solution USP is contraindicated in women who are or may become pregnant during therapy. If this drug is used during pregnancy, or if the patient becomes

pregnant while using this drug, the patient should be appraised of the potential hazard to the fetus.
Fluorouracil Topical Solution USP is also contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS:
Application to mucous membranes should be avoided due to the possibility of local inflammation and ulceration. Additionally, cases of miscarriage and a birth detect (ventricular septal defect) have been reported when fluorouracil was applied to mucous membrane areas during pregnancy.
Occlusion of the skin with resultant hydration has been shown to increase precutaneous penetration of several topical preparations. If any occlusive dressing is used, there may be an increase in the severity of inflammatory reactions in the adjacent normal skin. A porous gauze dressing may be applied for cosmetic reasons without increase in reaction.
Exposure to ultraviolet rays should he minimized during and immediately following treatment with Fluorouracil Topical Solution USP because the intensity of the reaction may be increased.
PRECAUTIONS
General: There is a possibility of increased absorption through ulcerated or inflamed skin.
Information for Patients: Patients should be forewarned that the reaction in the treated areas may be unsightly during therapy and, usually, for several weeks following cessation of therapy. Patients should be instructed to avoid exposure to ultraviolet rays during and immediately following treatment with Fluorouracil Topical Solution USP because the intensity of the reaction may be increased. If Fluorouracil Topical Solution USP is applied with the fingers, the hands should be washed immediately afterwards. Fluorouracil Topical Solution USP should not be applied on the eyelids or directly into the eyes, nose or mouth because irritation may occur.
Laboratory Tests: Solar keratoses which do not respond should be biopsied to confirm the diagnosis.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil. Studies with 5-fluorouracil have shown positive effects in *in vitro* tests for mutagenicity and on impairment of fertility.
5-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 immunosurpressed 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* (i.e., chromatid gaps, breaks and exchanges) in Chinese hamster fibroblasts at concentrations of 1.0 and 2.0 □g/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 with this product

Doses of 125 to 250 mg/kg, administered intaperitoneally, 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.

Pregnancy: Pregnancy: **Teratogenic Effects: Pregnancy Category X:** See **CONTRAINDICATIONS** section.

Nursing Mothers: It is not known whether fluorouracil is excreted in human milk. Because there is some systemic absorption of fluorouracil after topical administration (see **CLINICAL PHARMACOLOGY**), because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue use of the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The most frequent adverse reactions to Fluorouracil Topical Solution USP occur locally and are often related to an extension of the pharmacological activity of the drug. These 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 (ventrictdar septal defect) have been reported when fluorouracil was applied to mucous membrane areas. Leukocytosis is the most frequent hematological side effect.

Although a causal relationship is remote, other adverse reactions which have been reported infrequently are:

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.

OVERDOSAGE

There have been no reports of overdosage with fluorouracil.
The oral LD_{50} for a 5% fluorouracil topical cream was 234 mg/kg in rats and 39 mg/kg in dogs. These doses represented 11.7 and 1.95 mg/kg of fluorouracil, respectively. Studies with a 5% fluorouracil topical solution yielded an oral LD_{50} of 214 mg/kg in rats and 28.5 in dogs, corresponding to 10.7 and 14.3 mg/kg of fluorouracil, respectively. The topical application of a 5% fluorouracil cream to rats yielded an LD_{50} of greater than 500 mg/kg.

DOSAGE AND ADMINISTRATION

When Fluorouracil Topical Solution USP is applied to a lesion, a response occurs with the following sequence; erythema, usually followed by vesiculation, desquamation, erosion and reepithelialization.
Fluorouracil Topical Solution USP should be applied preferably with a nonmetal applicator or suitable glove. If Fluorouracil Topical Solution USP is applied with the fingers, the hands should be washed immediately afterward.
Actinic or Solar Keratosis: Apply Fluorouracil Topical Solution USP, 2.5% twice daily in an amount sufficient to cover the lesions. Medication should be continued until the inflammatory response reaches the erosion state, at which time use of the drug should be terminated. The usual duration of therapy is from 2 to 4 weeks. Complete healing of the lesions may not be evident for 1 to 2 months following cessation of therapy.

HOW SUPPLIED

Fluorouracil Topical Solution USP is available in 10 mL drop dispensers containing 2.5% (NDC 0000-0000-00) fluorouracil on a weight/weight basis.
Store at 25°C (77°F); excursion permitted to 15°C - 30°C (59°F - 86°F).

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