CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-985

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20-985 SUBMISSION DATE: 10/28/99

PRODUCT: [redacted] Cream, 0.5%
(fluorouracil cream)

SPONSOR: Dermik Laboratories, Inc.
Collegeville, PA 19426

REVIEWER: Veneeta Tandon, Ph.D.

NDA Review

I. BACKGROUND

Drug Classification: 3S

Dosage Form: Topical Cream

Indication: For topical treatment of multiple actinic or solar keratosis of the face and the scalp.

Drug Class: Antineoplastic agent containing a fluorinated pyrimidine. Fluorouracil interferes with the synthesis of DNA by competitively inhibiting thymidylate synthetase. To a lesser extent it inhibits the formation of 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.

Dose and administration: The cream should be applied to the face once daily for at least 1 week in an amount sufficient to cover the lesions.

Foreign Marketing History: 0.5% 5-fluorouracil (5FU) cream is not marketed in any country. A topical 5FU solution and cream in concentrations of 1% (Fluoroplex®) as well as 2% (Efudex® -solution only) and 5% (Efudex®) are currently marketed in the U.S. for actinic keratoses. Fluorouracil is also given as an intravenous injection at a dose of 4 mg/kg for 4 days, with daily dose not to exceed 800 mg per day for the treatment of breast and gastrointestinal malignancies.

Formulation: 5FU is [redacted] in a methyl methacrylate/ [redacted] glycol dimethacrylate [redacted] (Microsponge®) [redacted] with

dimethicone, as a ——— As a component of the drug product formulation, the 5FU in the Microsponge® is designated as 5FU Acrylates ——— and contains ——— of 5FU on a w/w% basis. The other ingredients and its composition is listed in the following table.

Ingredient	Quantity w/w %
5-Fluorouracil	
Carbomer 940, NF	
Glycerine, USP	
Polyethylene Glycol 400, NF	
Polysorbate 80, NF	
Sorbitan monooleate, NF	
Octyl hydroxy sterate —	
Methyl Gluceth-20, —	
Stearic Acid, NF	
5-FU in acrylates ———	
— Dimethicone in acrylates ———	
Trolamine, — , NF	
Propylene Gylcol, USP	
Methyl Paraben, NF	
Propyl Paraben, NF	
Purified water, USP	

II. RECOMMENDATION

The sponsor has demonstrated lower but not proportionate systemic exposure of fluorouracil as 0.5% cream compared to the currently marketed 5.0% Efudex® cream. The information provided in this application meets the requirements of the Office of Clinical Pharmacology and Biopharmaceutics. The recommendation of adding the standard deviation to the plasma and urine pharmacokinetic parameters as suggested in the "Label" section of the review should be conveyed to the sponsor.

TABLE OF CONTENTS

I. Background..... 1
Drug Classification..... 1
Dosage Form..... 1
Indication..... 1
Drug Class..... 1
Dosage and Administration 1
Foreign Marketing History..... 1
Formulation..... 1
II. Recommendation..... 2
III. Analytical Validation..... 3

IV. Pharmacokinetic Studies..... 4
Multiple dose study..... 4
V. In Vitro Permeation Studies..... 7
Comparison of Dermik and Efudex formulation at a concentration of — 7
Comparison of various Dermik formulations..... 10
VI. Overall conclusions..... 11
VII. Label 11
VIII. Appendix..... 13

III. ANALYTICAL VALIDATION

A new assay methodology was developed for this NDA. The methodology used for the analysis of 5FU in Efudex® was based on radioactivity. But this assay could not differentiate between radiolabeled 5FU and its radiolabeled metabolites. Hence, a new ——— method was developed, the validation of which is summarized below.

IV. PHARMACOKINETIC STUDIES

- **Has the systemic absorption of 5-fluorouracil (5FU) been evaluated under maximal use and maximal exposure conditions in patients?**
- **Is 5FU systemically absorbed upon topical application in patients?**
- **How does the systemic exposure of 0.5% 5FU cream (to-be-marketed) compare to the 5.0% 5FU cream already marketed in US?**

The sponsor has conducted a multiple dose study (up to 28 days) to yield steady state conditions and to maximize systemic exposure to the drug in patients with actinic keratosis and actinic damage. It was anticipated that up to four weeks administration of either product (0.5% 5FU or the marketed 5% Efudex®) would produce a maximum amount of tolerable facial irritation and would likely increase absorption of the drug and is also consistent with the proposed usage for this product. The study is summarized below. The conclusions at the end of the study summary will answer the questions raised.

A pharmacokinetic multiple dose study of 5FU in patients with actinic keratosis treated with either 5FU (0.5%) topical cream or Efudex® (5.0%) topical cream (Study DL-6025-9720)

The Dermik 0.5% 5FU (lot no. 970080) was administered once daily (as per the proposed labeling for this product) and Efudex® 5% was administered b.i.d. (as per the approved label for the product). Four weeks of Efudex® is also consistent with its labeling.

Clinical Site

Analytical Site

The sponsor has used a formulation of 5FU that contains ——— as a component of the ——— used. It was later determined that due to the interaction between 5FU and — the stability batches were unsatisfactory. Hence, the sponsor decided to remove — from the formulation. The formulation with — was also used in the Phase III studies. An in vitro experiment (described in the next section) demonstrates the similarity in skin permeation from formulations with or without the ———

Twenty patients (14M & 6F) completed this study. A total of 11 patients received the Dermik treatment and 10 patients received the Efudex® treatment. A 1 gm dose of Dermik 5FU (Lot 970080) was applied in the morning for 28 days (maximum of 28 doses) to the affected area of the face and/or anterior bald scalp. Similarly, a 1 gm dose of Efudex® (lot 0744) was applied in the morning and evening for up to 28 days (maximum of 5 doses) to the affected areas of face and/or anterior bald scalp. Subject demographics are attached in the Appendix on page 14.

The sponsor chose Efudex® as the comparator in this study, due to past experience of only radiolabeled Efudex®. Previous studies with Efudex® demonstrated measurable exposure to 5FU, hence Efudex® arm in this study would assure as a positive control as the new assay method adopted could detect 5FU.

The pharmacokinetics of 5FU were assessed on the last day of a multiple dosing schedule in both plasma and urine of the patients. Plasma samples were taken at predose, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post final dose. Urine samples were taken on Day 28 or the day of the final application over the following intervals: predose, 0-2 hours, 2-4 hours, 4-8 hours, 8-12 hours and 12-24 hours. 5FU was analyzed in the plasma and urine by [redacted] assays with LOQs of [redacted] ng/ml and [redacted] ng/ml, respectively.

Plasma Concentrations

Three patients receiving Dermik 0.5% 5FU had detectable concentrations of 5FU, with a single patient having sufficient data points in order to calculate pharmacokinetic parameters. The Cmax observed ranged from [redacted] ng/ml.

The pharmacokinetic parameters from the one patient receiving 0.5% Dermik cream for 28 days is listed below.

Patient	Cmax (ng/ml)	Tmax (hr)	AUC(0-t) (ng.hr/ml)
7	0.768	0.996	2.803

Following Efudex® 5% cream, 9 patients had detectable plasma concentrations, with 6 having sufficient data points in order to calculate pharmacokinetic parameters. The Cmax ranged from [redacted] ng/ml. The Tmax of 1 hr was similar between the two formulations.

The pharmacokinetic parameters from the 6 patients is given in the following table.

APPEARS THIS WAY
ON ORIGINAL

Patient	Cmax (ng/ml)	Tmax (hr)	AUC(0-t) (ng.hr/ml)
1	10.4	1.075	14.507
4	5.26	1.031	21.578
9	8.34	0.999	20.528
11	5.05	1.017	21.788
22	27.20	1.027	37.518
23	12.7	1.000	18.42
Mean	11.492	1.025	22.390
SD	8.242	0.028	7.890

The final 1 g dose of Dermik 0.5% 5FU and 5% Efudex® provided 5 and 50 mg doses respectively. Based on this there should be approximately a 10 fold difference in exposure. With just one patient in the 0.5% Dermik cream group with AUC values, it is difficult to conclude the difference in level. However, with this one subject compared to the mean AUC from the Efudex® group, it does fall in this range (AUC 2.8 vs. 22.4 ng.hr/ml).

The mean plasma concentration-time profile for 5FU for the two treatment arms is attached in the Appendix on page 15.

Urine Concentrations

For the Dermik 0.5% cream, the mean Cum Ae over 24 hours was 2.737 µg with a maximum excretion rate — µg/hr. For Efudex® 5% cream, the mean Cum Ae over 24 hours was 119.833 µg, with a maximum excretion rate of — µg/hr. The maximum excretion rate occurred during the 0-2 hour interval post final dose.

The individual subject Cum Ae and maximum excretion rate is tabulated in the following table for the individual subjects for both the Dermik and Efudex® formulation and the mean cumulative urine 5FU versus time profile is attached in the Appendix on page 15.

Dermik 0.5% Cream			Efudex 5% cream		
Patient	Cum Ae(µg)	Max Excr. Rate(µg/h)	Patient	Cum Ae(µg)	Max Excr.Rate(µg/h)
2	0.0		1	89.599	
3	0.7		4	123.398	
7	9.5		6	34.202	
10	1.579		8	0.000	
12	0.455		9	197.214	
13	0.000		11	62.555	
15	0.000		14	93.124	
19	15.022		20	90.810	
21	0.000		22	329.866	
24	0.000		23	177.562	
Mean	2.737		Mean	119.833	
SD	5.221		SD	94.804	

There appears to be approximately a 40-fold greater difference in the Cum Ae between the Dermik and Efudex® group. Ideally, there would have been a 10-fold difference based on the difference in dose.

The data suggests that in terms of applied dose of 5FU, 0.055% of the applied final 1 g dose of 0.5% Dermik cream was excreted in the urine and 0.24% of the 1 g dose of 5% Efudex® cream was excreted in the urine. Investigators have suggested that less than 10% of the systemically available 5FU is excreted in the urine. Based on this urinary excretion data, there is a 0.55% (0.055%x10) systemic absorption of 5FU from the Dermik cream and 2.4% (0.24%x10) from the 1 g dose of the Efudex® cream. The systemic absorption is 5.96% based on the package insert of Efudex®. The original Efudex® study was a ^{14}C radiolabeled study, which did not distinguish between parent and metabolites, this could have been one of the reasons for the difference along with the difference in analytical methodology.

Conclusions

- Dermik 5FU 0.5% cream has low measurable plasma concentrations for fluorouracil in only 3 of the 11 subjects when administered under steady state conditions designed to maximize exposure in patients with actinic keratosis. These concentrations were lower than those obtained with the Efudex® 5.0% cream.

- The estimated cumulative urinary excretion of 5FU in urine was lower with the 0.5% Dermik formulation, compared to the 5% Efudex® cream, even when normalized for differences in doses administered.

V. IN VITRO PERMEATION STUDIES

- **How does the in vitro permeation compare between the Dermik formulation (i.e. Microsponge system) and to-be-marketed Efudex® formulation?**
- **Is the permeation of the formulation used in PK and clinical studies (with) the same as that intended to be marketed (without)?**

The sponsor has conducted two in vitro experiments that are summarized below.

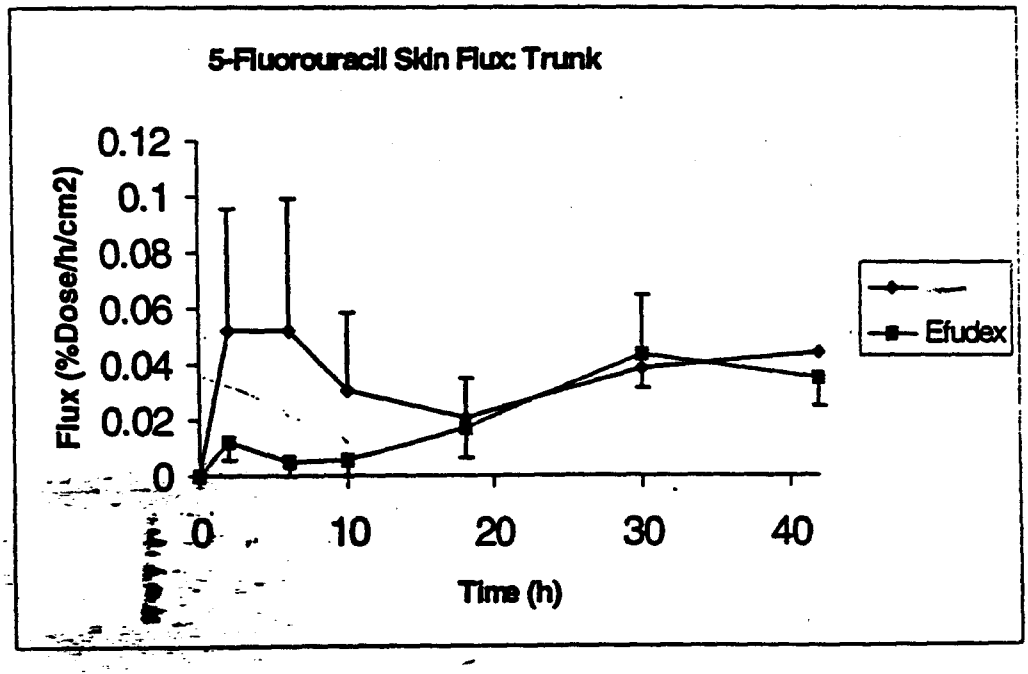
In vitro permeation of 5FU from two topical formulations (cream and Efudex 5% cream) in human cadaver skin (Study DL 6025-9522)

The two formulations were compared along with the comparison between two different body sites (trunk skin vs. leg skin) using Franz cells.

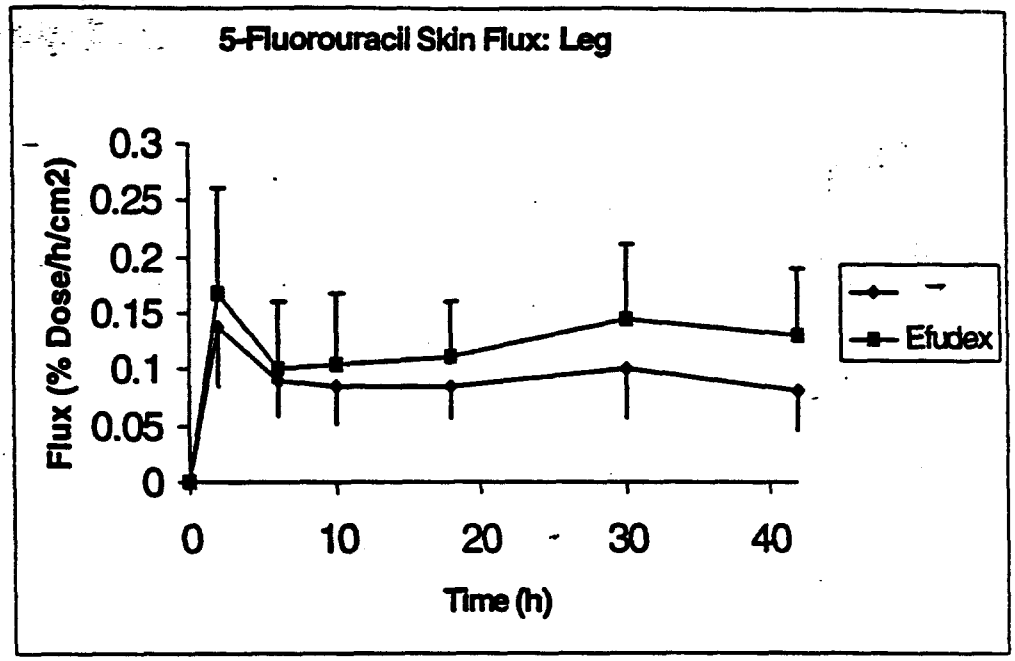
Human skin from 7 donors (3 trunk skin and 4 leg skin) dermatomed to a thickness of approximately 0.25 mm was used in this study. This study was intended to measure flux of 5FU through the skin over 48 hours as well as absorption of 5FU into different skin layers at the end of the 48 hour period. In this study both 5FU formulations

Total penetration was determined by measuring drug concentrations at 4, 8, 12, 24 36 and 48 hours. Drug concentrations were measured using with a LOQ of µg/ml.

Drug flux through the cadaver skin in shown in the following figures. The data is attached in the Appendix on pages 16-17.



APPEARS THIS WAY
ON ORIGINAL



Total drug penetration and localization of the drug in the dermal and epidermal layers of the skin is tabulated in the following table.

Parameter	Dermik (% of dose)	Efudex® 5% (% of dose)
Total penetration (Flux into receptor chamber)		
Leg	3.35	4.43
Trunk	1.51	0.83
Epidermal		
Leg	7.06	5.19
Trunk	2.20	0.60
Dermal		
Leg	0.72	0.70
Trunk	0.94	2.53

APPEARS THIS WAY
ON ORIGINAL

Conclusions

- Penetration through human skin of 5FU from both formulations was rapid, with an initial peak flux occurring within 5 hours of it application and a secondary peak occurring at 30 hours after application in both leg and trunk skin.

- Flux of 5FU from either formulation through the leg skin was quite similar, with a slightly greater flux for Efudex® formulation. Conversely, there was greater total flux for the Dermik formulation than the Efudex® formulation when evaluated using trunk skin. This is primarily due to the differences in the rate in the first 18 hours.

- Total penetration was higher in leg skin as compared to the trunk skin.

- Vast majority of the applied dose (>95%) remained at the surface of the skin and was recoverable in the surface wash at 48 hours, regardless of the formulation and skin source.

Skin permeation of 5FU from cream formulations (Study Dl 6025-9726)

In this study, three formulations of ^{3}H-labeled Dermik [redacted] 0.5% 5FU were compared. This study was designed to measure flux of 5FU through the skin over 24 hours, as well as absorption of 5FU into different skin layers at the end of 24 hour period. A forth formulation 5% Efudex® was also used for comparison in a radiolabeled form.

Skin was obtained from a single cadaver. The preparations differed with regard to the presence or absence of a [redacted] and the method of 5FU [redacted] onto the microsponge. These were:

0.5% 5FU,old [redacted] technique with [redacted] (DLC 031)
0.5% 5FU, old [redacted] without [redacted] (96K 033)
0.5% 5FU, new [redacted] without [redacted] (96L 034)
Efudex® Commercial product

Drug concentration was measured using [redacted] where each sample was counted for 5 minutes. The percent of 5FU absorbed is shown in the following table.

Formulation	Mean Amount Applied to the Skin (µg)	Mean total amount absorbed at 24 hr (µg)[1]	% Absorbed[2]	% Percent Remaining in the Skin[3]
DLC 031	25.7	0.712	2.77	86
96K 033	25.7	0.863	3.36	87
96L 034	23.8	0.854	3.59	92
Efudex	255	5.62	2.20	55

[1]sum of amounts in stratum corneum, viable skin and receptors
[2]Amt absorbed/Amt applied
[3]Amts in the stratum corneum + viable skin/total amt absorbed at 24 hours

Conclusions

- All three Dermik formulations performed similarly in terms of absorption through the skin, though they differed regarding the presence or absence of the ——— and the method of ——— the 5FU onto the microsponge excipient.

- Efudex® (5%) at 10 times the concentration resulted in approximately 7 times the flux through the skin and total amount absorbed. This implies that there is potentially greater systemic exposure with the Efudex® formulation. However when absorption was normalized (as a % of applied dose), total absorption (%) was similar among all formulations.

- Distribution of absorption differed between Dermik and Efudex® formulation. Greater percentages (86-92%) of the absorbed dose remained within the skin layer at 24 hours with the Dermik formulation compared to 55% with Efudex®. Since the site of drug action in the treatment of actinic keratosis is within the skin lesion itself, it would be the amount of drug remaining in the skin that would be therapeutically important.

VI. OVERALL CONCLUSIONS

- There was lower systemic exposure in patients treated with 0.5% Dermik cream as compared to the marketed 5% Efudex® cream.

- In vitro studies have demonstrated that percutaneous absorption of 0.5% Dermik cream was not affected by the presence of absence of the ——— or the method of ———

- All 0.5% Dermik formulations were retained larger percent amounts of absorbed 5FU within the skin layers as compared to the Efudex® formulation.

- Absorption of 5FU was site dependent, with the legs showing more absorption than the trunk. However, the site of treatment with the Dermik 5FY 0.5% cream is the face and the scalp, hence this information is not of much relevance to the current application. Possible differences in absorption with the change in application sites should be borne in mind ———

VII. LABEL

It is recommended to included standard deviations for the plasma and urine pharmacokinetic parameters in the summary table given in the "Pharmacokinetics" section of the label. The label provided by the sponsor is acceptable with the addition of

standard deviations. The standard deviations can be obtained from pages 5and 6 of the review.

/S/ 4/20/2000

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D /S/ 5/11/00

CC: NDA 20-985
HFD-540/Div File
HFD-540/CSO/Lutwak
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

APPEARS THIS WAY
ON ORIGINAL

APPENDIX
NDA 20-985

APPEARS THIS WAY
ON ORIGINAL

Appendix 16.2.4.1 Demographics

Patient Number	Patient Initials	Date Of Birth	Age (yrs)	Gender	Race	Frame	Height (in)	Weight (lb)
1	[redacted]	[redacted]	72	Male	Caucasian	Small	66.0	130.0
2			64	Male	Caucasian	Medium	72.9	206.0
3			61	Male	Caucasian	Large	70.0	187.0
4			58	Male	Caucasian	Medium	68.5	186.0
5			56	Male	Caucasian	Large	72.3	202.0
6			57	Male	Caucasian	Medium	73.0	160.0
7			75	Male	Caucasian	Medium	69.0	179.0
8			66	Male	Caucasian	Medium	67.5	182.0
9			54	Male	Caucasian	Small	66.3	124.0
10			66	Male	Caucasian	Medium	70.5	170.0
11			64	Male	Caucasian	Large	66.5	203.0
12			63	Male	Caucasian	Large	71.2	196.0
13			71	Male	Caucasian	Medium	71.2	207.0
14			71	Male	Caucasian	Medium	67.0	156.0
15			78	Male	Caucasian	Small	73.0	196.0
16			62	Female	Caucasian	Medium	60.5	172.0
20			57	Female	Caucasian	Large	65.5	217.0
21			60	Female	Caucasian	Large	66.0	166.0
22			65	Female	Caucasian	Large	66.2	165.0
23			67	Female	Caucasian	Medium	66.0	141.0
24			66	Female	Caucasian	Medium	62.0	140.0

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Figure 3

Mean Plasma 5-Fluorouracil Concentrations Versus Time

Semi-Log Scale

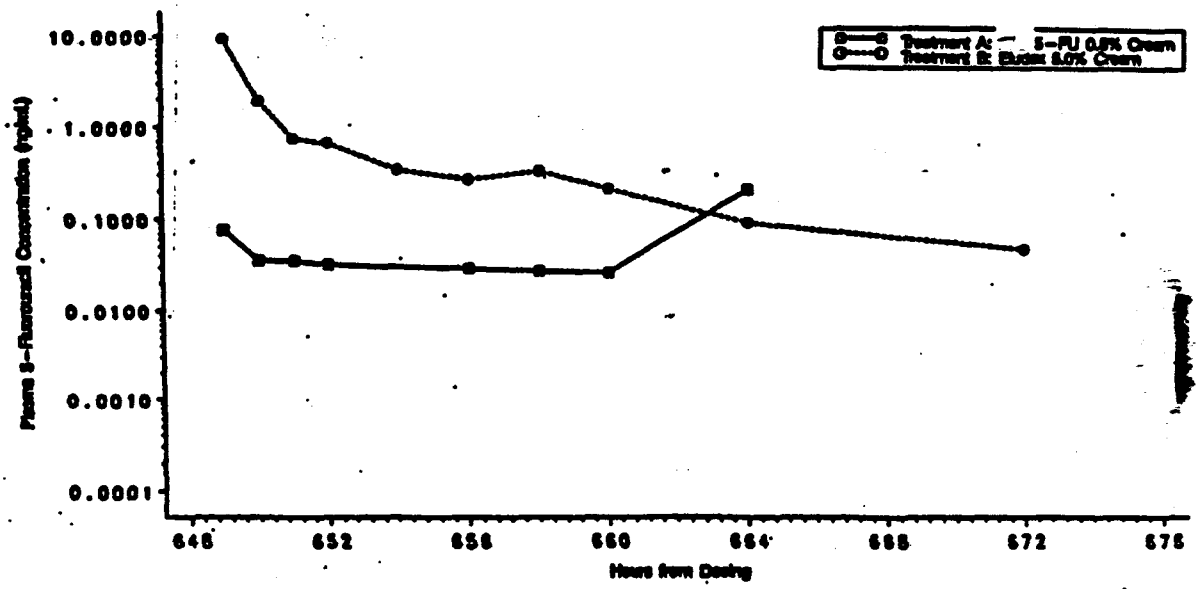


Figure 25

Mean Cumulative Urine 5-Fluorouracil Amount Versus Time

Linear Scale

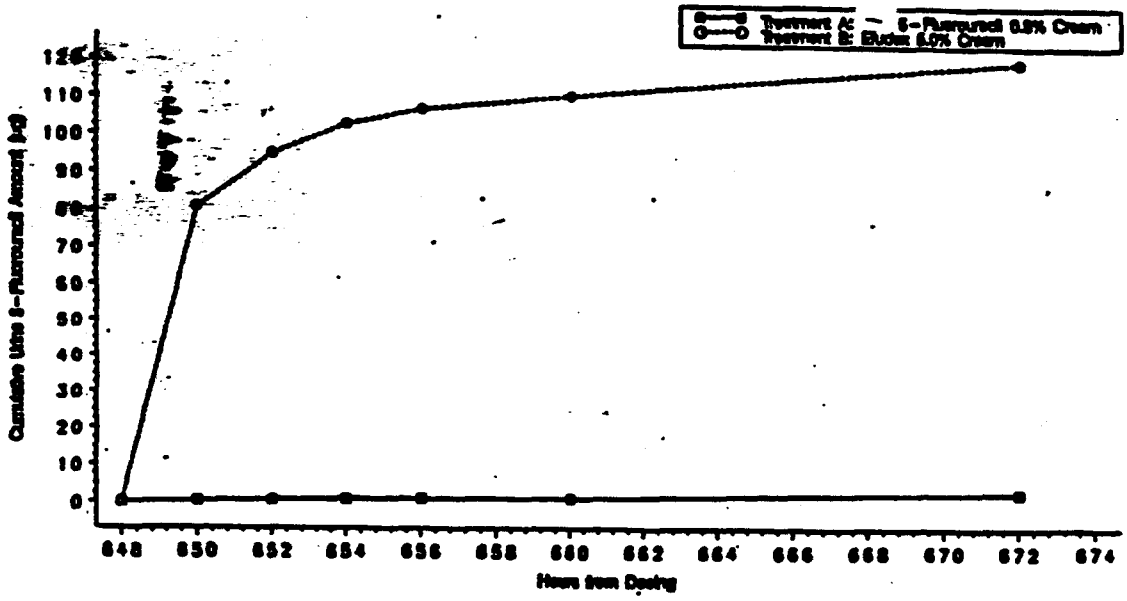


Table 2: Rate of Penetration and Mass Balance of 5-Fluorouracil in Human Cadaver Trunk Skin

(Receptor values are µg/hr/cm^2, Mass Balance values are µg)

Sample Source	Mean[a]	SE	% Dose[b]	Efudex 5% Mean	Efudex 5% SE	Efudex 5% % Dose
1. 2 hr Receptor	0.238	0.197		0.044	0.022	
2. 6 hr Receptor	0.240	0.214		0.018	0.018	
3. 10 hr Receptor	0.142	0.127		0.022	0.022	
4. 18 hr Receptor	0.093	0.063		0.045	0.023	
5. 30 hr Receptor	0.169	0.072		0.145	0.038	
6. 42 hr Receptor	0.199	0.129		0.122	0.035	
Total Penetration	6.41	4.25	1.51	3.27	1.05	0.83
Dermis	4.00	1.78	0.94	10.01	0.30	2.53
Epidermis	9.35	0.84	2.20	2.36	0.33	0.60
Surface Wash	419.87	28.85	98.79	378.53	7.40	95.83
Total Recovery	439.63	23.72	103.44	394.17	6.33	99.79

a: Mean and SE values from three donors each in triplicate determinations.
b: % Dose determined from mean application across donors of formulation (8.5 mg — 7.9 mg Efudex; see Appendix A) and assuming — formulations.

Table 3: Rate of Penetration and Mass Balance of 5-Fluorouracil in Human Cadaver Leg Skin

(Receptor values are µg/hr/cm^2, Mass Balance values are µg)

				Efudex 5%		
Sample Source	Mean[a]	SE	% Dose[b]	Mean	SE	% Dose
1. 2 hr Receptor	0.544	0.190		0.565	0.371	
2. 6 hr Receptor	0.359	0.181		0.361	0.256	
3. 10 hr Receptor	0.337	0.178		0.381	0.266	
4. 18 hr Receptor	0.345	0.166		0.417	0.203	
5. 30 hr Receptor	0.426	0.237		0.543	0.283	
6. 42 hr Receptor	0.353	0.193		0.496	0.252	
Total Penetration	14.76	6.84	3.35	18.17	9.83	4.43
Dermis	3.18	0.55	0.72	2.86	1.85	0.70
Epidermis	31.08	2.62	7.06	21.28	6.02	5.19
Surface Wash	474.36	61.68	107.81	446.83	95.63	108.98
Total Recovery	523.37	58.22	118.95	488.50	61.92	119.15

a: Mean and SE values from three donors each in triplicate determinations.
b: % Dose determined from mean application across donors of formulation (8.8 mg — , 8.2 mg Efudex; see Appendix A) and assuming ——— formulations.