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Re: Citizen Petition Requesting FDA Not to Approve Any ANDA for a Generic Version of Efudex® that Does Not Include Data from a Comparative Clinical Study Conducted in Patients with Superficial Basal Cell Carcinoma
Docket No. 04P-0557

Rothwell, Figg, Ernst & Manbeck ("Rothwell Figg") submits these comments in opposition to the above-referenced Citizen Petition filed by Valeant Pharmaceuticals International ("Valeant") on December 21, 2004 ("the Valeant Petition") requesting that the Food and Drug Administration ("FDA") require abbreviated new drug applicants for generic versions of Efudex® (fluorouracil) Cream to perform comparative clinical endpoint studies in patients with superficial basal cell carcinoma ("BCC") as a condition of approval. The Valeant Petition claims that comparative studies in patients with actinic keratosis ("AK") should not be used as a basis for demonstrating bioequivalence between the brand and generic product.

Rothwell Figg respectfully submits that the Valeant Petition should be denied for at least the following reasons.

First, Efudex® Cream is approved for the topical treatment of AK and the treatment of BCC when conventional methods are impractical, such as multiple lesions or difficult treatment sites. According to IMS data from 2002 through June of 2005, just over 60% of the Efudex® prescriptions were for use in AK versus only slightly more than 1% of the prescriptions for use in BCC. (Appendix 1). Thus, for every one patient who uses Efudex® to treat basal cell carcinomas, sixty patients use Efudex® to treat AK. This highly pertinent fact appears nowhere in Valeant's Citizen Petition.

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Efudex® Use for BCC and AK Based upon IMS Data

	2002-2003	2003-2004	2004-2005	Avg percent
Actinic Keratosis	60.1%	66.8%	60.3%	62.4%
Basal Cell Carcinoma	1.4%	0%	2%	1.13%

Second, both the courts and the FDA have acknowledged that neither the FDA statute nor its implementing regulations require an ANDA applicant to submit studies for each indication. The FDA statute merely states that “the Secretary may establish alternative, scientifically valid methods to show bioequivalence.” 21 U.S.C. 355(J)(8)(C). Thus, the statute requires that ANDAs must demonstrate bioequivalence, but it does not prescribe the precise methodology or standards to be used by FDA to assure bioequivalence. Rather, the FDA has the discretion to determine the appropriate bioequivalence standards based on the characteristics and approved uses of the product. The FDA has wide discretion to determine the most appropriate mechanism for demonstrating bioequivalence in topical drug products - - a point Valeant does not contest.

Third, comparative studies in patients with AK should be used as a basis for demonstrating bioequivalence for the approved indications of Efudex®. Valeant’s argument that bioequivalence must be demonstrated for each site of action ignores the fact that both AK and BCC are located in the epidermis. In addition, Valeant’s argument that AK and BCC appear at exclusively different sublayers is not supported by the scientific literature. Finally, Valeant’s sublayer argument ignores the fact that BCCs usually grow upward and coexist in the same sublayer(s) as AK. See Section II, below.

Fourth, Valeant’s argument that BCC studies are required because the comparative clinical bioequivalence studies must be performed in the “most difficult to treat” condition is not supported by the facts. The Efudex® label itself, NDA approval documents, and a recent journal article demonstrate that there is no evidence that BCC is the more difficult to treat condition. See Section III, below.

Fifth, Valeant’s reliance on the studies required with respect to other products that are used to treat AK and BCC is misplaced. The first two products contain significantly lower levels of fluorouracil and the third product includes a different active ingredient. See Section V, below.

Sixth, Valeant’s extended discussion outlining FDA’s historical perspective that in vitro testing such as pharmacodynamic and pharmacokinetic studies are typically not satisfactory tools to demonstrate equivalence of two formulations is not relevant to the studies required to demonstrate equivalence of fluorouracil cream. FDA has clearly stated that comparative clinical studies are necessary to support approval of a generic version of Efudex. Therefore, the

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discussion on in vitro test methods has no bearing on the ANDA approval requirements for fluorouracil cream.

I. THE MMA DOES NOT REQUIRE A COMPARATIVE CLINICAL STUDY CONDUCTED IN PATIENTS WITH BCC

Valeant argues that the Medicare Prescription Drug, Improvement, and Modernization Act (“MMA”) requires comparative clinical studies in patients with BCC to demonstrate the bioequivalence of a generic version of Efudex® Cream. Citizen Petition at 8-9. This is simply not correct.

The language of the MMA merely confirms FDA’s nearly two decades old practice with respect to drugs that are not intended to be absorbed into the bloodstream and did not change FDA’s approval requirements for topical drugs. The pertinent statutory language provides:

(ii) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action.

(C) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

21 U.S.C. 355(j)(8)(A)(ii) and 21 U.S.C. 355(j)(8)(C) (emphasis added).

Section 1103(b) of House Report 108-391 specifically states that “[t]he amendment made by subsection (a) does not alter the standards for approval of drugs under section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(j).” (Appendix 2). Thus, the new language did not alter FDA’s long standing approach with respect to bioequivalence of drugs that are not intended to be absorbed into the bloodstream – the FDA determines the appropriate approach based on the specific facts of each case. Therefore, the statutory language does not prohibit approval of a non-systemically absorbed drug product based on a single clinical endpoint study nor was the MMA language intended to change FDA’s requirements.

Moreover, the courts and the FDA have clearly acknowledged both: (1) that a clinical study is not required for each indication; and (2) that the FDA is accorded discretion in determining scientifically valid approaches for determining bioequivalence:

Under 21 CFR 320.24(a) and (b)(4), FDA ‘may require in vivo or in vitro testing, or both, to establish . . . the bioequivalence of specific drug products,’ including ‘. . . appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence.’ Neither the statute nor the regulations require an applicant to submit comparative clinical trial data for each separate disease indication before FDA may approve an ANDA. It is well-accepted that FDA has wide discretion to determine how the bioequivalence requirement is met; FDA’s discretion need only be based on a ‘reasonable and scientifically supported criterion, whether [the agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs...’ (Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 218 (D. D.C. 1996) (quoting Schering Corp. v. Sullivan, 782 F. Supp. 645, 651 (D. D.C. 1992), vacated as moot sub nom, Schering Corp. v. Shalala, 995 F.2d 1103 (D.C. Cir. 1993))). Thus a comparative clinical trial to establish bioequivalence with the RLD in each labeled indication is not required by the Act or its implementing regulations.

Westwood Squibb Pharmaceuticals, Inc., Citizen Petition Response dated April 22, 2002. Docket No. 95P-0379P/CP1 at 3-4 (emphasis added).

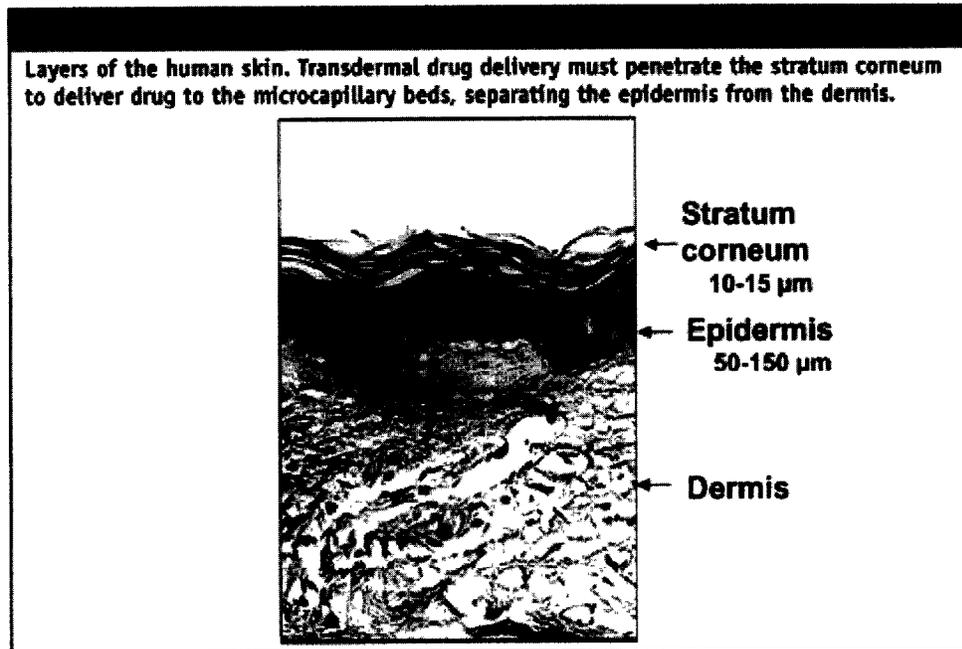
II. COMPARATIVE STUDIES IN PATIENTS WITH AK SHOULD BE USED AS A BASIS FOR DEMONSTRATING BIOEQUIVALENCE IN PATIENTS WITH BCC

The Valeant Petition argues that bioequivalence must be demonstrated for each site of drug action. Citizen Petition at 9-11.

The location of both AK and BCC is the epidermis. The epidermis is a thin layer that ranges in thickness from 0.05 mm – 0.15 mm. In addition, the older the patient, the thinner the epidermis becomes. Efidex® Cream is used predominately in patients over 60 years of age. **Thus, as shown below, the location of both AKC and BCC is the epidermis (that is, the same “site”).**

Valeant argues that AK and BCC occur at different “sites” because they may be found in different sublayers of the epidermis. It is generally accepted that within the thin layer of the epidermis there is cell differentiation that forms four sublayers, and each sublayer is only a few hundredths of a millimeter thick. The sublayers of the epidermis are illustrated in the following figure:

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Source: <http://www.drugdeliverytech.com/cgi-bin/articles.cgi?idArticle=63>

As acknowledged in the Valeant Petition (page 4), the stratum corneum is the primary barrier for penetration by topical drug products. Once a drug penetrates the stratum corneum, the primary limitation to penetration through the epidermis has been eliminated.

Valeant argues that AK and BCC appear in exclusively different sublayers within the epidermis. But the cellular sublayer for the appearance of AK and BCC is not so clear cut. Anderson, N.J., Jeffes, E., *New Therapeutic Advances: Skin Cancer and Actinic Keratoses*, *Skin & Allergy News*, 2003:34:9-14 (“[h]istopathologically, AK’s demonstrate a localized proliferation of atypical keratinocytes in the basilar keratinocytes or at the dermal-epidermal junction”)(Appendix 3); <http://www.aad.org/professionals/Residents/MedStudCoreCurr/DCActinicKer-NoMelCancer.htm> (“[m]icroscopically, one sees large keratinocytes with atypical nuclei in the lower portion of the epidermis”) (Appendix 4).

Valeant argues that AK usually originates in the stratum spinosum, the layer that immediately adjoins the deepest layer of the epidermis, the stratum basale, where BCCs often originate. However, rather than recognizing that BCCs usually grow upward and coexist in the same sublayer(s) as AK, the petitioner focuses on the ‘downward’ growth that represents tumors for which Efidex® Cream is not usually indicated.

Valeant’s focus on downward growth is contradicted by its own label, which states under Indications and Usage:

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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%.

(Appendix 5). Therefore, the package insert itself cautions that for diagnoses of any basal cell carcinoma that has downward growth (and is thereby not considered a superficial BCC), surgery - - not Efudex® Cream - - should be the method of treatment. Thus, Valent focuses on a condition for which Efudex® Cream is not indicated as its principal support for its argument that there are two distinct sites of action.

Valeant also argues that penetration from the squamous to the basal sublayer (which are physically joined) raises substantial questions regarding the bioequivalence of two formulations that have been demonstrated to be therapeutically equivalent in an AK trial. Valeant's argument ignores the fact that there is no evidence to suggest that penetration will not be the same at adjoining levels and also fails to acknowledge that when fluorouracil cream is used as indicated, the BCC tumor will normally grow upward through the squamous sublayer. The following photograph from an American Academy of Dermatology article illustrates the superficial BCC moving up into the upper layers of the epidermis. (Appendix 4).



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In summary actinic keratoses may arise in the stratum spinosum but on biopsy extend into the basilar layer, while BCC begin in the basilar layer but extend upward for superficial BCC's. Therefore they are in the same site of action for 5-flurouracil.

In addition, Valeant also argues that FDA's recent decision to approve Metvixia for AK, but not for BCC, is evidence that a study must be performed in patients diagnosed with BCC. Citizen Petition at 10. But Metvixia is not chemically the same as Efudex®, nor does it have essentially the same formulation or comparable physico-chemical properties as would a generic version of Efudex®. Thus, the decision to not approve Metvixia for BCC has no bearing on the requirements for products that are pharmaceutically equivalent and bioequivalent to Efudex®.

III. AK IS MORE DIFFICULT TO TREAT THAN BCC

Valeant argues that bioequivalence must be demonstrated in the most difficult to treat condition, which it incorrectly maintains is BCC. Citizen Petition at 11-13.

Valeant's argument that BCC is the more difficult condition to treat ignores the approved labeling for Efudex® which states that 93% of the superficial BCC tumors treated with Efudex® Cream or Solution were successfully treated. (Appendix 5).

According to the Summary Basis of Approval for NDA 16-831 dated June 4, 1970, "[t]here were 197 cases of actinic keratosis treated with 5% 5-flurouracil cream formulation of which 167 (84%) showed 'complete clinical response.'" (emphasis added) (Appendix 6).

A recent article published in the *Journal of Drugs and Dermatology* described studies performed with Efudex® versus Carac® (0.5% 5-fluorouracil in a microsphere bead formulation) and reported that after twice daily applications for 4 weeks Efudex® cleared 88.8% of actinic keratosis:

	% Reduction of AKs	Proportion of patients with 100% clearance
5% microsphere	86.2%	50%
2.5% microsphere	95.1%	71.4%
0.5% microsphere	92%	66.7%
<u>5% Efudex®</u>	<u>88.8%</u>	47.6%
Vehicle (Placebo)	26.6%	0%

(Appendix 7). Therefore, Valeant's claim that superficial BCC (with a 93% success rate) is more difficult to treat than Actinic Keratosis (with an 84% to 88.8% success rate) is without merit.

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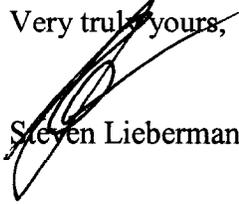
V. THE CURRENT STATE OF THE ART DOES NOT REQUIRE STUDIES IN PATIENTS WITH BCC

Valeant argues that the FDA's study requirements for other products support similar study requirements for ANDAs for generic versions of Efudex® Cream. Citizen Petition at 13-14. Carac® and Fluoroplex® contain 0.5% and 1% fluorouracil compared to 5% for Efudex®. The fluorouracil products cited contain only 10% and 20% of the amount of the active ingredient contained in Efudex®, respectively. The third product, Aldara®, contains a different active ingredient altogether. Hence, there is no reason to conclude that the tests that were required for these products should also be required for generic versions of Efudex® Cream. It is noted that Aldara® is now approved for certain BCCs.

CONCLUSION

FDA has the authority and expertise to determine the appropriate type of comparative clinical studies to demonstrate bioequivalence of generic versions of Efudex® Cream. A comparative clinical study in AK patients can clearly provide scientific evidence of bioequivalence for the approved indications for Efudex®. This approach is fully supported by the statutory language. Therefore, Valeant's Petition should be denied.

Very truly yours,



Steven Lieberman

SL/MB/gsw

Enclosures

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APPENDIX 1

Copyright IMS HEALTH									
NPA Plus - Monthly Rx Audit, NDTI									
Numbers Are In Thousands (000)s					Total Rx		MAT JNE/03		2002-2003
					MAT JNE/03 TRx	MAT JNE/03 TRx DUA MAT JNE/03	MAT JNE/03 TRx DUA% MAT JNE/03		
EFUDEX 1187 VLT					339	339	100	Total Actinic Kerat	
702003 KERATOSIS SENILIS						175	51.6	60.10%	
V67070 SURG AFT SKIN DISORD OTH						40	11.9		
V67014 SURG AFT MAL NEO SKIN						8	2.3		
V67076 SURG AFT VEN WART						8	2.5		
078107 PLANTAR WARTS						14	4.1		
V67031 SURG AFT OTHER EYE DISOR							0		
701110 KERATOSIS						21	6.3		
078101 VERRUCA						5	1.6		
709902 LESION SKIN NOS						6	1.9		
370205 PHOTOKERATITIS NOS						2	0.7		
173903 MAL NEO OF UNSP SITE						8	2.4		
173904 MAL NEO BASAL CELL CARCI						5	1.4		
078106 VENEREAL WARTS							0		
173905 MAL NEO SQUAMOUS CELL CA						2	0.7		
692702 DERMATITIS ACTINIC						5	1.5		
187401 MALIG NEOPLASM OF PENIS							0		
757320 POROKERATOSIS							0		
272202 XANTHELASMA							0		
V67078 SURG AFT CONGEN MALF							0		
140901 MAL NEOPLASM OF LIP UNSP						1	0.2		
172901 MAL MEL NEVUS							0		
173301 MAL NEOPLASM OF FACE OTH						4	1.1		
173302 MALIG NEO OF CHEEK SKIN						2	0.7		
173304 MALIG NEO OF NOSE SKIN						1	0.2		
173307 MAL NEO OF FOREHEAD						3	1		
173401 MAL NEO OF SCALP + NECK						5	1.4		
173601 MAL NEO SKIN UPPER LIMB							0		
195002 CANCER FACE NOS							0		

Copyright IMS HEALTH										
NPA Plus - Monthly Rx Audit, NDTI										
Numbers Are In Thousands (000)s							Total Rx			
							MAT JNE/03 TRx	MAT JNE/03 TRx DUA MAT JNE/03	MAT JNE/03 TRx DUA% MAT JNE/03	2002-2003
623001 DYSPLASIA VAGINA								4	1.2	
629902 DIS OF FEMALE GEN ORG NO								8	2.5	
701101 KERATODERMA NOS								7	1.9	
799902 DIAGNOSIS NOT STATED								4	1	
Note: Actinic Keratosis = keratosis senilis +										
keratosis +										
Photokeratosis +										
Dermatitis Actinic										

APPENDIX 2

House Report 108-391 - MEDICARE PRESCRIPTION DRUG, IMPROVEMENT, AND
MODERNIZATION ACT OF 2003

SEC. 1103. BIOAVAILABILITY AND BIOEQUIVALENCE.

(a) IN GENERAL- Section 505(j)(8) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(8)) is amended--

(1) by striking subparagraph (A) and inserting the following:

`(A)(i) The term `bioavailability' means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

`(ii) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action.'; and

(2) by adding at the end the following:

`(C) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.'

(b) EFFECT OF AMENDMENT- The amendment made by subsection (a) does not alter the standards for approval of drugs under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)).

[http://www.congress.gov/cgi-bin/cpquery/R?cp108:FLD010:@1\(hr391\)](http://www.congress.gov/cgi-bin/cpquery/R?cp108:FLD010:@1(hr391))

APPENDIX 3



A SUPPLEMENT TO

Skin & Allergy News*

Vol 34, No. 3

MARCH 2003

New Therapeutic Advances: Skin Cancer and Actinic Keratoses

**Update on
Melanoma**

**Common
Nonmelanoma
Skin Cancers:
Basal Cell
Carcinoma and
Squamous Cell
Carcinoma**

**Actinic
Keratoses: Current
Approaches to
Management**

**5-Fluorouracil
Therapy:
Clinical Tips
and Issues**

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Actinic Keratosis: Current Approaches to Management

Nancy J. Anderson, MD, and Edward W. Jeffes III, MD, PhD

Actinic keratoses (AKs) are the third most frequent reason for dermatologist office visits, accounting for more than 10% of outpatient visits.¹ It has been known for some time that the presence of AKs identifies patients who are at high risk for the development of other skin cancers, particularly squamous cell carcinoma (SCC).²

Pathogenesis and Natural History

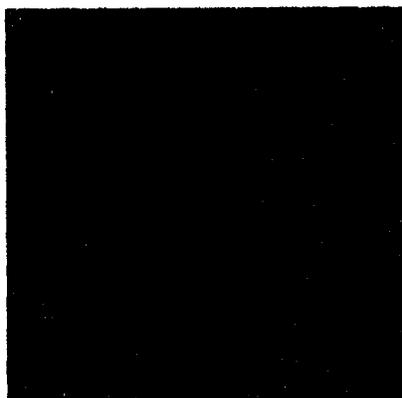
More recently, the relationship between AKs and SCC has become more clearly defined. There is growing acceptance that AKs represent a progression along a spectrum from a benign to a malignant skin lesion.³ At one end of the spectrum are AKs that represent thin, well-differentiated SCC, followed by thicker, well-differentiated SCC, and finally, the thickest lesions that would be called well-differentiated SCC according to both the current and older terminology. One estimate is that approximately 8% of AKs will progress over a period of 10 years.⁴ Some experts maintain that an AK lesion may be viewed as analogous to cervical intraepithelial neoplasia⁴ and that AKs should be considered a precursor to invasive, well-differentiated SCC.

In fact, AKs are localized neoplasms limited to the skin. In the strictest sense, there is good evidence to support the view that they are well-differentiated SCC lesions in situ with a good prognosis.⁵ Histopathologically, AKs demonstrate a localized proliferation of atypical keratinocytes in the basilar keratinocytes or at the dermal-epidermal junction. When atypia penetrates to more than one third to one half of the dermis, or if it extends through the full thickness of the epidermis, most pathologists would characterize the lesion as an SCC lesion.

Most AKs do not progress to SCC, and many AKs spontaneously regress. The possibility of regression and the fact that not all AKs progress to SCC have

led some insurance carriers to argue that AKs do not require treatment. However, at present, it is not possible to identify with certainty which AKs will regress, which will fail to progress, and which will progress to SCC.

It is the opinion of these authors that hypertrophic or hyperkeratotic



AKs are high-risk lesions for progression to SCC or are already well-differentiated SCCs. It is important to note that well-differentiated SCC has a metastatic rate of 0.5%-3% (often quoted as 1%) in healthy, immunocompetent individuals. Poorly differentiated SCCs are uncommon, but they carry a very guarded prognosis because they may be associated with an aggressive course, metastasis, and death.

SCCs that develop in burn or radiation scars or in scars at sites of draining osteomyelitis are associated with a metastatic rate in the range of 10%-30%. Actinic cheilitis—AKs of the mucous membrane epithelium, usually on the lower lip when it converts to

SCC—are at high risk for metastasis, with a reported rate of 11%.⁶

Epidemiology and Risk Factors

The prevalence of AK is between 11% and 26% in the general population, but prevalence and incidence vary with age and skin type. Individuals with fair skin, light-colored eyes, and red or blond hair are at highest risk for photodamage and the development of AKs. Those with Fitzpatrick skin types IV, V, or VI have intrinsic sun protection equivalent to a sun protection factor rating of 2-3, a level sufficient to prevent most AKs.

The risk for AKs also increases with cumulative sun exposure, and, therefore, AKs are seen more frequently with increasing age. For example, more than 80% of fair-skinned individuals over 70 years of age have AKs.⁷

Accumulating evidence shows that immune status is an important risk factor for the development of AKs. The incidence of AKs is higher in patients who undergo long-term immunosuppression following solid organ transplantation or the long-term use of immunosuppressants, such as cyclosporine, for other reasons. The cumulative increase in risk for skin cancer—mainly SCC—increases with duration of immunosuppression: 7% after 1 year, 45% after 11 years, and 70% after 20 years of immunosuppression.⁸ Finally, the inability to repair damaged DNA in the skin cells has been identified as a factor associated with the development of AKs.

Diagnosis of AKs

Typical AKs are hyperkeratotic scaling papules and plaques. Often, in an area in which a solitary or only a few AKs are visible, a larger field of AKs can be perceived to the touch. The anatomic distribution reflects the expected pattern of sun exposure: More than 80% of AKs occur on the upper limbs, head, and neck.⁷ A number of clinical variants to this typical presentation also may be seen, most commonly including hypertrophic AK, pigmented AK, and actinic cheilitis (see **Figure**).⁹

Any erosion on the lower lip (actinic cheilitis) should be biopsied prior to starting therapy. In contrast to a shave excision (which usually is not done to a sufficient depth), a 3-mm punch biopsy at the margins of the ulcer provides an appropriate amount of tissue for examination. Biopsies also should be performed if there is suspicion that an AK has progressed to invasive SCC. The changes that suggest possible evolution of AKs to SCC are pain, erythema, ulceration, induration, hyperkeratosis, increasing size, and cutaneous horn formation.^{10,11}

Treatment of AKs

Choosing a Modality

Because of the risk for progression to

invasive SCC, the American Academy of Dermatology has issued guidelines that recommend that AKs be eliminated. The factors to consider in choosing therapy include (1) the medical status of the patient; (2) the size, location, number, and duration of the lesions; (3) whether a change has occurred in the growth pattern of the lesions; (4) previous treatment; and (5) the clinician's and patient's experience with a given technique.^{12,13}



Commonly Used Treatments

Among the most commonly used treatments are cryosurgery, electrodesiccation and curettage (E&C), and topical 5-fluorouracil (5-FU). Cryosurgery is appropriate for solitary lesions and is associated with a high cure rate and generally acceptable cosmetic results. The

disadvantages of freezing AKs are pain during treatment and the possibility of sensory loss. Hypopigmentation is not uncommon with cryosurgery, so this may not be a good choice for cosmetically sensitive areas such as the face. The risk for hypopigmentation can be minimized by using a freeze-thaw cycle of about 20-30 seconds per lesion to create intercellular ice crystals and avoid damage to melanocytes.

When a lesion is not definitively established as an AK by clinical examination, E&C is a good option because it provides a specimen for malignancy testing. It is also associated with a high cure rate. The patient should be cautioned, however, that scarring and hypopigmentation may occur.

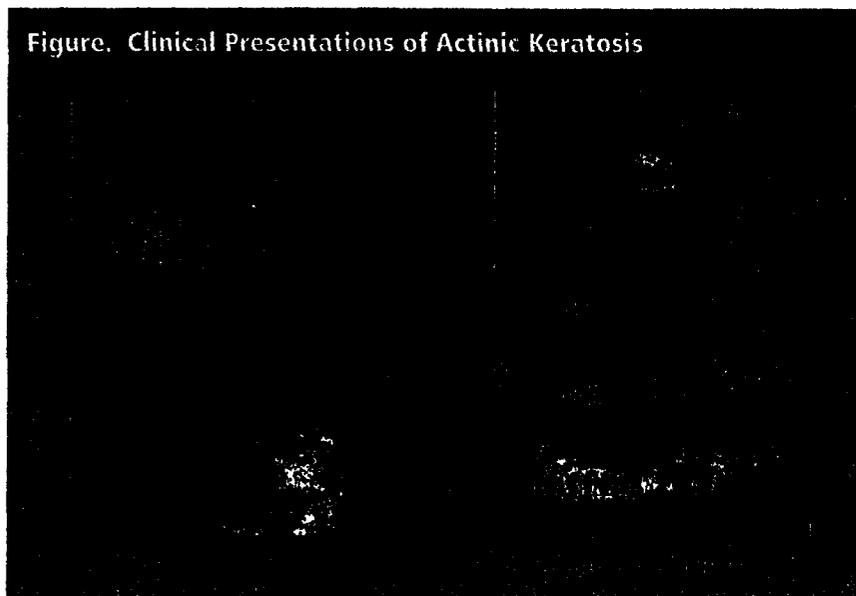
5-FU is a pyrimidine analogue that is incorporated into the cells' DNA because of its structural similarity to uracil. The drug interferes with DNA synthesis by blocking conversion of deoxyuridylic acid to thymidylic acid.^{14,15} It selectively affects damaged cells associated with clinical and subclinical AKs, sparing healthy tissue.^{14,16} The cure rate with 5-FU is highly dependent on the appearance of inflammation.^{17,18} A disadvantage of 5-FU therapy is the response of photodamaged skin: erythema, edema, and discomfort. However, inflammation, erythema, edema, erosion, and ulceration are likely necessary for full efficacy. Patients who understand this are more apt to accept the response as a sign of therapeutic efficacy and to be less disturbed by discomfort and the unsightly appearance of the skin during treatment.

5-FU cream and solution are available in a variety of strengths (0.5%, 1%, 2%, and the most often-used concentration, 5%). The response that indicates efficacy, as described above, may be related to the concentration.^{17,18}

Newer Topical Treatment Options

Several other modalities have been studied and are being used to treat AKs. The nonsteroidal antiinflammatory drug diclofenac sodium is now available

Figure. Clinical Presentations of Actinic Keratosis



in topical form, a gel with 3% concentration of the drug. The mechanism of action in the treatment of AKs is unknown. The gel is applied to lesions twice daily for 2-3 months. Lesion healing may not be evident until 1 month posttreatment; up to 47% of patients have shown complete clearance of AKs at 30 days after cessation of therapy.

The results of a phase II study of imiquimod show that application of this topical immune response modifying agent may result in complete clearance of 50% of AKs treated 3 times weekly for 6 weeks. (A phase III study is nearing completion, but no data are yet available.)

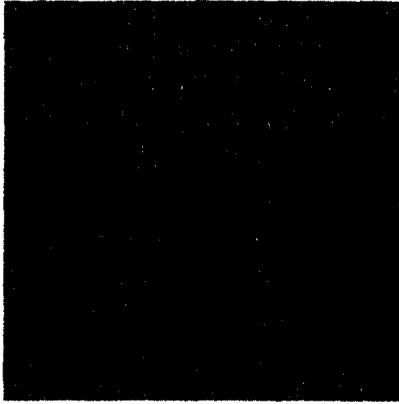
Topical retinoids are approved or are expected to be approved soon by the U.S. Food and Drug Administration (FDA) for the treatment of precancerous lesions, to mitigate fine lines, and to increase collagen production. These are applied daily or every other day.

Chemical peeling with 10%-25% trichloroacetic acid or phenol also has been used. Finally, laser surgery—for example, laser resurfacing with carbon dioxide ultrapulse—has shown reduction of precancerous lesions.

Photodynamic Therapy

In 1999, photodynamic therapy (PDT) with aminolevulinic acid (ALA) and a photosensitizing light source was approved by the FDA for the treatment of AKs. ALA—a precursor to the photosensitizing agent protoporphyrin IX (PPIX)—is applied to lesions on the scalp and face. When the treated skin is exposed to wavelengths ranging from 405-635 nm, the PPIX is photoactivated. Once activated, PPIX generates singlet oxygen and other activated oxygen species that damage cells. For this reason, it is important that ALA be applied directly to the AKs, with normal skin avoided.

Burning and stinging are common during the photoactivation phase, and 71% of patients in clinical trials had scaling and crusting (an expected therapeutic response). However, more than 98% of patients who begin PDT are able to complete the treatment.



Conclusion

Actinic keratosis accounts for 10% of dermatologist office visits. In the strictest sense, AKs are considered to be well-differentiated SCC in situ with a good prognosis. AK lesions present as hyperkeratotic scaling papules and plaques. Prevention is best accomplished with sun-protective measures described in the article on melanoma (page 3).

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5-Fluorouracil Therapy: Clinical Tips and Issues

Edward W. Jeffes III, MD, PhD

Treatment with 5-fluorouracil (5-FU) has been a mainstay of topical therapy for actinic keratoses (AKs) for more than 3 decades. In that time, a large body of literature and countless clinical

encounters have resulted in the development of methods for minimizing side effects, enhancing patient comfort and compliance, and maximizing efficacy.

Dosing Considerations to Reduce Irritation

The usual dosing schedule for treating AKs on the head and neck is 5% 5-FU cream twice daily for 2 weeks. This leads to significant localized effects and, sometimes, confluent edema. Usually, the first week of treatment is well tolerated by all patients; most of the clinical effects begin by the start of the second week of treatment. During the second week, most patients experience discomfort and are bothered by their appearance due to the inflammatory response. For the first week following cessation of 5-FU applications, appearance is still a significant problem. By the second week after cessation of therapy, most of the scaling and crusting and much of the erythema have resolved.

Controlling the frequency and duration of 5-FU applications allows for improved control of the desired cutaneous reaction. A number of years ago, most clinicians treated AKs with 5% 5-FU twice daily for 4 weeks. The cutaneous reactions resulting from 4 weeks of such treatment are quite severe, commonly leading to confluent crusting and significant burning and stinging. Further, the cosmetic problems associated with this treatment schedule persist throughout therapy and last for at least 3 weeks after cessation of applications of the medication. To decrease the severity of erythema, crusting, and pain, topical corticosteroid creams are commonly used.

In general, the more erythema and crusting the patient can tolerate, the better the clinical response (a decrease in

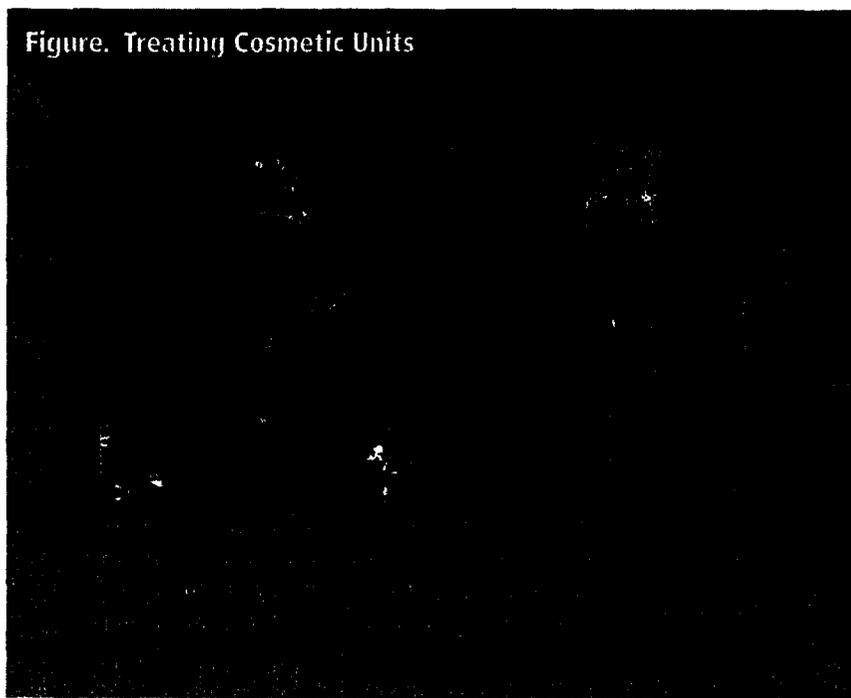
AKs). A twice-daily schedule of 5% 5-FU applications given for 2 weeks is better tolerated than when the duration is 4 weeks, but the 4-week schedule may be superior to a single 2-week course in eliminating AKs. However, if a 2-week course is repeated a second time, results may occur that are similar to the reaction seen with one 4-week course, thus allowing for greater patient tolerance while yielding the desired therapeutic effect.

Treatment of *cosmetic units*—treating different parts of the face or body at different times—is one method of increasing patient comfort with and tolerance of 5-FU treatment. Cosmetic unit treatment is particularly useful with balding men who have numerous

AKs of the scalp and forehead as well as lesions elsewhere on the face and head. I recommend daily or twice-daily applications of the medication on the bald scalp and forehead for 2 weeks. During this time, the treated area can be covered with a hat. The 2-week therapy gives the patient experience with the desired effect before the cheeks and ears are treated (see Figure).

Stepped therapy is another approach. One would start with once-daily applications of 1% or 2% 5-FU and, after a few weeks, increase the applications to twice daily. After several additional weeks, 5% 5-FU would be substituted for the lower concentration. Alternatively, one could have the patient use

Figure. Treating Cosmetic Units



the low-concentration 5-FU for 2 weeks, allow the skin to heal, and then reinstitute treatment with the 5% concentration. As with the cosmetic unit approach, stepped therapy gives the patient an opportunity to adjust to the effects of 5-FU treatment.

Marrero and Katz¹ reported success with a technique known as fluor-hydroxy pulse peel, in which the patient is treated with a 75% glycolic acid peel for 2 minutes, followed immediately by a single application of a 5% 5-FU solution. This regimen is repeated weekly for 8 weeks. Patients experienced transient erythema and scaling. This combination decreased the AK count in this study by 92% at the 6-month follow-up, compared with a 20% reduction in AK count with 75% glycolic acid peel alone.

Managing Effects of Therapy

Unless 5-FU applications result in significant erythema and crusting, the clinical effects are less than optimal. Patients with the most severe reactions experience not only the most complete AK resolution but also are left with skin that is smoother and less mottled. Thus, rather than side effects, erythema and crusting are more properly referred to as desired effects of treatment.

Patients who are applying 5-FU to the face can be advised to wash the treated area twice daily with a mild antibacterial cleanser such as chlorhexidine gluconate to minimize the occurrence of pustules. Ointments should be avoided, particularly if pustules are present, to prevent occluding these lesions and, possibly, increasing the risk for infection. At the start of therapy, patients can be given a prescription for an antihistamine and an analgesic (such as acetaminophen) to be filled if symptoms require.

Some clinicians give patients a prescription for oral antibiotics (to be filled only when needed). Because 5-FU treatment breaks the skin barrier, it is possible for staphylococci and streptococci to

infect the skin and cause pyoderma or cellulitis. However, infections are not a problem in the vast majority of patients treated with 5-FU. They are seen most commonly in patients who experience the most severe reactions, especially those on 4-week treatment regimens. Patients should be instructed to return for evaluation if they experience symptoms such as unusually severe pain or erythema.

Contact dermatitis occurs very rarely with 5-FU treatment. Contact dermatitis can be difficult to distinguish from the expected photodamaged-skin response to 5-FU. To test for allergic



contact dermatitis to 5-FU, have the patient apply the medication to a small area of skin that has not been photodamaged—the bathing trunk area is ideal—twice daily for 1 week. A reaction in the test area indicates contact dermatitis.

Periorbital edema may occur during and after treatment with 5-FU on the forehead and scalp. This results from the normal distribution of the transudate that results from the inflammatory reaction. Clinically significant periorbital edema is uncommon and usually resolves rapidly after cessation of treatment.

Patient Counseling

Patients must be educated about the desired effects of therapy and the relationship between short-term therapeutic response and short- and long-term overall efficacy. Literature provided by product manufacturers can be very helpful,

but usually is not sufficient. Many patients either do not read the brochures or do not fully appreciate the message even when shown photos of the desired response. Consequently, a follow-up visit at 2 weeks after the start of 5-FU applications can be critical to treatment success. At the follow-up visit, patients who are having a more severe reaction than is optimum can be treated. Those whose response is progressing as desired can be reassured that their appearance is what is expected for a good therapeutic outcome, and the expectation can be reiterated that their appearance will improve remarkably within a few weeks after stopping therapy.

Postmarketing Safety Data

In 2000, 440,000 prescriptions were written for 5% and 2% formulations of 5-FU; 95% of these were for the 5% concentration. A total of 27 adverse events were associated with the use of these concentrations of 5-FU. This is within the range of 25-30 cases of adverse events per year that have been reported for the previous 31 years in which 5-FU has been marketed in the United States. For the first 11 months of 2001 (the last date for which statistics are available), 29 adverse events were reported. With an estimated total of 13.6 million prescriptions, the adverse-event incidence is 1:14,672.

Most adverse events reported in 2000 were inflammatory symptoms, including burning, crusting, erythema, irritation, pain, itching, scarring, and ulceration. These occurred during treatment and usually resolved within 2 weeks after cessation of therapy. Interestingly, most of these are effects that have become recognized as desirable to long-term efficacy.

The theoretical risk for systemic toxicity is low for 5% and 2% 5-FU concentrations with twice-daily application. At most, 5%-10% of topically administered 5-FU is absorbed after application to the face and scalp. Metabolic elimination is rapid, with a

primary half-life of less than 10 minutes. There have been only 7 reports of possible systemic absorption and associated systemic toxicity (mainly bone marrow toxicity) in the 31 years since 5-FU was introduced. In four cases, patients had neutropenia, including decreased platelet counts; two patients had gastrointestinal ulcerations; and one case was reported of neutropenia with gastrointestinal symptoms and dihydropyrimidine dehydrogenase (DPD) deficiency. No deaths have been associated with systemic toxicity. In all cases, the symptoms resolved after 5-FU treatment was discontinued. The postmarketing data suggest that the incidence of systemic toxicity is 1:1.9 million prescriptions.

A new formulation of 5-FU was introduced recently, a 0.5% 5-FU cream in a microsp sponge delivery system. The product is approved for daily application for up to 4 weeks. The complete response rate after 4 weeks of treatment is reported as 48% (compared with a complete response rate of greater than 80% with the 5% concentration of 5-FU). In the clinical trials, erythema was reported in more than 90% of treated patients and 60% of those in the vehicle-only group. This reaction resolved to baseline within about 2 weeks after the end of treatment in all cases. The theoretical risk for systemic toxicity with this new formulation is very low, with no reports of observed toxicity in the phase III studies; to date, no postmarketing statistics on systemic toxicity are available.

A question has been raised regarding the safety of 5-FU in patients with DPD deficiency. Because DPD is the major enzyme employed to degrade 5-FU, a deficiency in the major pathway for 5-FU degradation logically would lead to the expectation that blood levels of the drug would be higher and that systemic toxicity might be a risk. As noted above, one

such case in a patient with DPD deficiency has been reported in the 31 years of experience with 5-FU. In this case, the patient was being treated for basal cell carcinoma. After 1 week of treatment, the patient experienced abdominal pain associated with bloody diarrhea and vomiting, as well as fever and chills. He was treated with broad-spectrum antibiotics and total parenteral nutrition. He gradually improved and recovered.



Johnson and Diasio² demonstrated that the association between DPD deficiency and severe toxicity is not clear in cancer patients treated with 5-FU intravenously at concentrations greatly exceeding those used with topical 5-FU therapy. In this study involving 103 patients with cancer—44 with DPD deficiency and 59 with normal DPD—Johnson found that the severity and rate of unexpected toxicity (including mucositis, granulocytopenia, and diarrhea) was comparable in the two groups. A slightly greater death rate was noted in the DPD-deficient group, for reasons that were not established. Thus, even at chemotherapy blood levels, DPD deficiency alone (either homozygous or heterozygous) does not predict severe toxicity.

The frequency in DPD deficiency in the general population is known: 3%-5% for heterozygous state and

0.1%-3% for homozygous state. One can assume that since 13.6 million prescriptions for 5-FU have been written, this represents approximately the same number of patients.

Conclusion

Topical 5% 5-FU is an effective treatment for AKs. Treatment is associated with crusting, edema, and other inflammatory effects that are associated with efficacy. The greater the inflammatory response, the more effective the therapy. However, consideration should be given to minimizing patient discomfort by using the strategies discussed here.

Topical 5-FU has a 31-year history of use, and the postmarketing surveillance data demonstrate that the risk for systemic toxicity is slight. Regarding the question of 5-FU therapy in patients with DPD deficiency, based on the data on the incidence of DPD deficiency in the general population cited above, 13,600 homozygous and 680,000 heterozygous DPD-deficient patients would have been treated in 31 years. Since only seven cases of systemic toxicity have been reported, the data suggest that DPD deficiency secondary to topical application of 5-FU probably is not a major problem. However, until the issue regarding the role of DPD in 5-FU toxicity has been resolved, it may be advisable to avoid the use of this drug in patients with DPD deficiency.

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APPENDIX 4

Actinic Keratoses and Non-Melanoma Skin Cancer

Thomas W. McGovern, MD and David J. Leffell, MD

Actinic Keratoses

The actinic keratosis (AK) is the earliest identifiable lesion that can eventually develop into an invasive squamous cell carcinoma (SCC). These lesions are diagnosed in 14% of all visits to dermatologists, following only acne and dermatitis in frequency. Debate swirls around the nomenclature for these lesions as some consider them "pre-cancerous" and others consider them to be a SCC confined to the lower portion of the epidermis. Actinic keratoses typically occur in fair-skinned individuals. In various northern hemisphere populations, 11-25% of adults have at least one, compared to 40-60% of adult Australians who live closer to the equator. One prospective study estimates that one AK/1000/year transforms into SCC, while retrospective studies predict that from 5-20% of all untreated AKs will progress to SCC. AK's are typically produced by ultraviolet radiation, but ionizing radiation, arsenic, or polycyclic hydrocarbon exposure may also cause them. At least two prospective studies have demonstrated that sunscreen reduces the likelihood of developing more AKs.

On physical examination, the typical AK is a poorly-demarcated, slightly erythematous papule or plaque found on sun-exposed areas such as the face, balding scalp, posterior neck, and dorsal upper extremity (Figure 1, Figure 2, Figure 3). Characteristically, AKs feel rough or "gritty" and may be difficult to see. Therefore, palpation of high-risk areas under an intense light source is essential to accurate diagnosis. Microscopically, one sees large keratinocytes with atypical nuclei in the lower portion of the epidermis. Liquid nitrogen, 5-fluorouracil cream, trichloroacetic acid, electrodesiccation and curettage, and CO2 laser can all eradicate AKs. Two newer treatment modalities include photodynamic therapy and the topical immunomodulator, imiquimod.

Non-Melanoma Skin Cancer

Non-melanoma skin cancer (NMSC) generally refers to the two most common cancers in the world: basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC). In 2003, there were an estimated 900,000-1,200,000 cases of NMSC (of which 75-80% were BCCs) in the United States, virtually equal in incidence to the 1,334,100 cases of all other cancers of all types combined. NMSC's account for approximately \$650 million in annual medical care in the United States. The primary risk factors for NMSC include skin phenotype, which determines one's ability to tan, and age, which is a proxy for total ultraviolet exposure. Other risk factors include smoking, immunosuppressed state, outdoor work, and tanning bed use. Organ transplant patients have an increased risk of SCC due to their medical immunosuppression (Figure 4). SCC incidence correlates best with total, lifetime ultraviolet radiation exposure, while BCC occurrence corresponds better with intermittent sunlight exposure and severe sunburns. Rates of NMSC increase with decreasing latitude, as SCC doubles for each 8-10 degree decline. The case-fatality rate for BCC is less than 0.05% and for SCC it is less than 0.7%. These rates have been decreasing for the last 20 years. Approximately 2200 Americans die annually from NMSC, and the vast majority of these die of metastatic SCC. Metastatic BCC is incredibly rare. After developing an initial BCC or SCC, patients have approximately a 50% chance of developing another NMSC within 5 years. For Americans born in 1996, the lifetime risk of developing NMSC is approximately 20%. Appropriate sun protection including hats, clothing and regular sunscreen are recommended for prevention of actinic keratoses and NMSC.

Superficial spreading BCC appears as a red, scaly, finely wrinkled plaque that may be confused with dermatitis (Figure 5 and Figure 6). The typical nodular BCC is a shiny or pearly, translucent papule with overlying telangiectases and rolled borders (Figure 7). Because the center often outgrows its blood supply, there may be a central, depressed ulcer with or without overlying hemorrhagic crust (Figure 8 and Figure 9). Infiltrative or morpheiform BCCs often feel indurated, resemble scars, and possess histologic margins far wider than would be suspected clinically (Figure 10). Microscopically a basal cell carcinoma is characterized by islands of intensely basophilic keratinocytes with peripheral palisading seen extending from the bottom of the epidermis or freely as islands in the dermis. In the more infiltrative types of BCC, thin strands of atypical cells are found within scar-like collagen.

Squamous cell carcinomas are generally erythematous, scaly papules or plaques with ill-defined borders (Figures 11, 12, 13, and 14), and they may be confused with large, hypertrophic AKs. It is often difficult to differentiate these AKs from early SCCs without a biopsy. Microscopically squamous cell carcinomas show a proliferation of pleomorphic keratinocytes confined to the epidermis (SCC in-situ) or extending into the dermis (invasive SCC).

Definitive diagnosis of NMSC requires a biopsy, and a shave, or tangential, biopsy is the preferred method. NMSCs may be treated with excision, electrodesiccation and curettage, liquid nitrogen, radiation, or topical imiquimod. Cure rate is 80-95% for BCCs or SCCs treated by these methods. Recurrent or large lesions, those located on high-risk areas or places where maximal normal tissue preservation is essential (such as the nose), and those with aggressive histologic patterns may be referred to a dermatologic surgeon for Mohs micrographic surgery. Mohs surgery achieves a 99% five-year cure rate for primary tumors and a 95% cure rate for recurrent lesions. With this technique, thin layers of tissue are excised and tumors are mapped under microscopic control. Further layers are excised only from areas that have tumor remaining.

All patients with skin cancer and actinic keratoses should protect themselves from sun exposure by the appropriate use of hats, protective clothing, sunscreens and avoidance of peak sunlight exposure. Approximately 60% of the cancer-causing ultraviolet rays reach the Earth's surface during a four-hour period centered on solar noon. The 'shadow-rule' is a simple rule-of-thumb for patients to remember: avoid direct sunlight when your shadow is shorter than you are.

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APPENDIX 5

EFUDEX®
(fluorouracil)
TOPICAL SOLUTIONS
AND CREAM

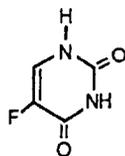
For Topical Dermatological Use Only
Not for Ophthalmic Use or Application
to Mucous Membranes, including Intravaginal Application

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, CO₂, 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 ¹⁴C-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 systemically. 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 CO₂ after 3 days of treatment with topically applied ¹⁴C-labeled fluorouracil.

INDICATIONS AND USAGE: Efudex is recommended for the topical treatment of multiple 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 the 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 embryoletality). 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 should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the DPD enzyme. DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities.

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 apprised 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 defect (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 be minimized during and immediately following treatment with Efudex because the intensity of the reaction may be increased.

Patients should discontinue therapy with Efudex if symptoms of DPD enzyme deficiency develop (see CONTRAINDICATIONS section).

Rarely, life-threatening toxicities such as stomatitis, diarrhea, neutropenia, and neurotoxicity have been reported with intravenous administration of fluorouracil in patients with DPD enzyme deficiency. One case of life-threatening systemic toxicity has been reported with the topical use of Efudex in a patient with DPD enzyme deficiency. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil.

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 afterward. 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/10T1/2 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

Drosophila 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.

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: 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 (ventricular 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 overdose with Efudex.

The oral LD₅₀ 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 LD₅₀ of 214 mg/kg in rats and 28.5 mg/kg in dogs, corresponding to 10.7 and 1.43 mg/kg of fluorouracil, respectively. The topical application of the 5% cream to rats yielded an LD₅₀ 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 stage, 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, hydroxypropyl 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); excursions permitted to 15°C – 30°C (59°F – 86°F).

ICN Pharmaceuticals, Inc.
Costa Mesa, CA 92626

NDA 16-831/S-047

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ICN Pharmaceuticals, Inc.

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3360097EX01

Rev. June, 2004

APPENDIX 6

NDA 16-831

June 4, 1970

Trip

SUMMARY OF BASIS OF APPROVAL

Drug Trade Name: Efudex

Established Names: 5-Fluorouracil Solution 2%
5-Fluorouracil Solution 5%
5-Fluorouracil Cream 5%

NDA Number: NDA 16-831

Firm's Name: Hoffmann-La Roche, Inc.
Nutley, New Jersey

Dosage Form: For topical application

Category or Use: Anti-neoplastic

I. Safety: Approval of this application for safety is based on the following studies:

A. Animal Studies: (See pharmacologist's review of NDA 16-831, Basis of Approval.)

B. Human Studies:

1. Human Pharmacology: As reported in the review of NDA 16-765, Dillaha et.al., measured percutaneous absorption using C¹⁴ labeled 5-Fluorouracil in a 5% ointment in 5 patients. He concluded that if 2 grams of the 5% ointment were applied daily, systemic absorption is in the order of 5-6 mg. (0.07 to 0.08 mg./Kg. per day).
2. Human patch tests: Repeat type patch tests were conducted in 200 individuals by William Epstein, M.D., using the cream and propylene glycol formulations. It is felt, as determined by patch tests for NDA 16-765, that positive reactions were of a primary irritant nature and probably due to the propylene glycol base.
3. Photosensitization Studies: As reported in the review for NDA 16-765, Frederick Urbach, M.D., of Temple University conducted studies in 85 normal volunteers and 5 patients with actinic keratoses. It was concluded that topical 5-Fluorouracil has no photosensitization potential. In addition, and as reported in NDA 16-765; an independent

study conducted by A. M. Kligman, M.D., of the University of Pennsylvania demonstrated no photosensitization potential using the scotch-tape stripping procedure and concentrations of 5-FU ranging from 0.5% to 20.0% in propylene glycol in ten male volunteers.

4. Special Studies: As reported in NDA 16-763, twelve normal volunteers applied the medication, 1% 5-Fluorouracil in propylene glycol to a four-square-inch area on the inner aspect of the arm for 14 days. Biopsies were taken from the treated and untreated areas. Histopathologic interpretation revealed no marked difference between the two areas.

II. Adverse Reactions: In the first submission, side effects were compiled for three formulations and listed as follows: First degree burn 1, burning of eyelids 2, burning and stinging 2, burning and tingling 2, dermatitis 1, pain 4, pruritus 1, pus formation 1, scarring 2, sore face 1, swelling and pain 1, tenderness 1, hyperpigmentation 1. Systemic reactions listed were: heart skipping 1, insomnia 1, menstrual irregularity 1, nausea 1, stomatitis 1, swelling and erosion of lips 1, taste of medicine 1. Laboratory abnormalities noted were: Eosinophilia 2, leukocytosis 3, decreased platelets 1, toxic granulation. (Total = 35).

In the second submission side effects were compiled as follows: burning 8, dermatitis 1, eyes watering 1, hyperpigmentation 8, pain 11, pruritus 15, scaling 1, scarring 2, soreness 1, sun sensitivity 1, tenderness 2, and discomfort 2. Other effects were irritability 1, leukocytosis 28. (Total = 82).

III. Efficacy:

- A. A meeting was held on January 27, 1970, in which three expert dermatologists were present. (See memorandum of meeting, January 27, 1970, and amendment to NDA dated February 18, 1970). The experts testifying on behalf of the sponsor were:

Dr. Edmund Klein, Chairman, Department of Dermatology, Roswell Park Memorial Institute and Professor of Dermatology State University of Buffalo Medical School.

Dr. Walter F. Lever, Chairman, Department of Dermatology, Tufts Medical School and Lecturer in Dermatology Harvard Medical School.

Dr. Clarence S. Livingood, Chairman Department of Dermatology, Henry Ford Hospital.

It was their unanimous opinion that post-treatment clinical observations are more meaningful than are post-treatment biopsies in the evaluation of the treatment of solar keratoses.

In addition, there are letters of testimony (amendment of February 18, 1970) from three other expert dermatologists which essentially reiterate the above. The names of these experts are listed as:

Dr. Rudolph F. Beer
Professor and Chairman, Department of Dermatology
New York University Medical Center

Dr. D. J. Demis
Professor of Dermatology
Albany Medical College

Dr. J. M. Knox
Professor and Chairman, Department of Dermatology
Baylor School of Medicine

B. The following "open label" studies were conducted:

1. There were 295 cases treated using 2% 5-Fluorouracil in propylene glycol of which 229 (78%) showed a "complete clinical response".
2. There were 215 cases treated with the 5% concentration of 5-Fluorouracil in propylene glycol of which 186 (86%) showed "complete clinical response".
3. There were 197 cases of actinic keratoses treated with 5% 5-Fluorouracil in cream formulation of which 167 (84%) showed complete clinical response.

C. Nine investigators conducted controlled studies using pre- and post-treatment biopsies in 63 patients using 1% 5-Fluorouracil in propylene glycol (NDA 16-765). As stated in the evaluation section in the Medical Officer Review for this NDA, there appears to be excellent correlation between clinical assessment and histopathologic assessment of the actinic keratoses treated. This would appear to confirm the opinion of expert testimony received in defense of the efficacy of topical 5-Fluorouracil.

IV. Controls: (See chemist's review of NDA 16-831, Basis of Approval).

cc:

Orig NDA

Dup NDA

~~Exp NDA~~ NYK-30

BD-100 BD-140 BD-200

BD-140/DAD/JBSanders/6-4-70/cbs

Typed/6-10-70/cbs

Revisions typed/6-30-70/wjs

1st R/D endorsed by JBSanders/6-9-70; NEMcQueen/6-9-70; & AXSmith/6-16-70

2nd R/D endorsed by JBSanders/6-30-70

John E. Sanders, M.D.

APPENDIX 7



5-1-06 Clearer
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TOPICAL TREATMENT OF ACTINIC KERATOSIS WITH FLUOROURACIL: IS IRRITATION ASSOCIATED WITH EFFICACY?

JOSEPH JORIZZO MD

WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA

Abstract

Actinic keratoses (AKs) are common dysplastic epidermal lesions that share clinical, histologic, and molecular features with squamous cell carcinoma. Therapeutic options include destructive modalities (i.e., cryosurgery, curettage) or topical fluorouracil treatment. The efficacy of topical fluorouracil for the treatment of widespread AK lesions has been demonstrated in multiple studies, but treatment is often associated with significant skin irritation. Various approaches to decrease irritation while maintaining efficacy have been attempted, including altered treatment regimens, combination therapies, and variations in vehicle formulations. Recently, a novel topical fluorouracil cream that contains 0.5% 5-fluorouracil in a microsphere vehicle has been approved for the treatment of AK. Data demonstrate that this low-dose formulation is effective in reducing AK lesions while maintaining a tolerable irritation profile.

Introduction

Actinic keratoses (AKs) are common dysplastic epidermal lesions that typically occur in fair-skinned individuals who are chronically exposed to intense sunlight¹³. Clinically, these lesions manifest as rough, scaly, variably erythematous patches, with surrounding areas often showing evidence of sun damage (i.e., broken blood vessels, discoloration, and blotchy pigmentation)²⁴. The prevalence of AK lesions increases with age and with cumulative ultraviolet radiation exposure. Rates are as high as 25% in various northern hemisphere populations and peak at over 60% among Australian adults^{2,44}.

Histologically, the AK lesion is characterized by atypical keratinocytes in which there is a loss of polarity, nuclear pleomorphism, and disordered maturation, all features common to squamous cell carcinoma (SCC)^{42,5}. In fact, AK lesions demonstrate features of malignancy from their inception, not only cytologically, but from a molecular biologic perspective as well⁴⁷. Specifically, AK lesions share identical p53 gene mutations with SCC⁴⁹. A review of 165 cutaneous SCC lesions demonstrated that 82% arose from or were in close proximity to an AK lesion⁶. In cutaneous SCC that has metastasized,

44% of the original lesions had contiguous AK lesions present histologically⁸.

Thus, AK is the initial pre-invasive manifestation of a continuum of clinical, histologic, and molecular abnormalities that can evolve to invasive (and metastatic) SCC⁴². Malignant conversion rates of AK have been reported to range from 0.1% to 10%⁴²; however, the potential for malignant progression can be affected by a number of patient-specific factors, including age and immunocompetency. Treatment of AK lesions is recommended to avoid potential progression to more aggressive malignancy¹⁰.

Efficacy and Tolerability of Topical Fluorouracil for the Treatment of AK

Numerous therapeutic options are available for AK. Destructive modalities such as cryosurgery, photodynamic therapy, electrodesiccation, and curettage are common treatment approaches for isolated AK lesions^{40,4}. However, topical fluorouracil is considered by many clinicians as the treatment of choice for extensive, widespread AK⁵. An additional advantage of topical fluorouracil is its potential to treat subclinical lesions that are commonly found in patients with significant skin damage³⁸.

Topically applied fluorouracil destroys AK lesions by blocking DNA synthesis. Specifically, fluorouracil inhibits thymidylate synthetase, the enzyme responsible for catalyzing the conversion of deoxyuridine-5 monophosphate to thymidine-5 monophosphate⁷. Because rapidly multiplying malignant or dysplastic cells synthesize more DNA than normal cells, fluorouracil has a more pronounced effect on their proliferation⁹. In addition, fluorouracil may alter the expression and metabo-

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lism of messenger RNA²⁰. Light and electron microscopic studies have demonstrated that actinically-damaged epidermis treated with fluorouracil is sloughed and replaced with healthy keratinocytes⁹.

Early studies evaluating topical fluorouracil demonstrated beneficial results in the treatment of AK lesions²¹. Topical fluorouracil, available commercially in the United States as a 1% solution or 1% cream (Fluoroplex[®], Herbert Laboratories), as a 2% or 5% solution, and as a 5% cream (Efudex[®], Roche Laboratories), is approved by the Food and Drug Administration for the treatment of AK lesions. Treatment regimens usually include twice-daily application for approximately 3 to 4 weeks. The effectiveness of topical fluorouracil in reducing the number of AK lesions has been established, but significant skin irritation accompanies efficacy in the majority of cases²²⁻²⁵. Although patients are encouraged by the high efficacy rates achieved with topical fluorouracil treatment, many of them reject therapy once shown the associated undesirable cosmetic side effects.

In an effort to decrease the irritation associated with topical fluorouracil therapy, altered treatment regimens, combination therapies, and variations in concentration strengths and vehicle formulations have been explored²⁶. In one such study Pearlman evaluated weekly "pulse" dosing with 5% fluorouracil solution²⁷. Patients applied 5% fluorouracil solution twice daily once a week until either all lesions were smooth or the patient reached a maximum of 9 weeks of treatment²⁷. Pulse therapy produced AK clearance rates of 96% to 100% in 10 patients, and the author concluded that weekly pulse dosing "...produces the same benefit with much less local irritation than the conventional daily dosing schedule."²⁷ However, in a study conducted by Epstein, neither efficacy nor decreased local irritation was associated with pulse topical fluorouracil therapy²⁸. A total of 13 patients applied 5% fluorouracil solution twice daily once a week, for a mean of 10.5 weeks. Of the 13 patients treated, 2 achieved excellent results, 3 achieved a good response, and 8 failed to demonstrate any improvement. Efficacy was linked with irritation: patients experiencing excellent results also experienced irritation scores of approximately 3 (i.e., marked erosions, not acceptable by any patient; Fig 1)²⁸.

In a combination study conducted by Breza et al, the efficacy and facial tolerance of topical fluorouracil with triamcinolone acetonide cream were evaluated²⁹. In this split-face study each patient was treated with 1% fluorouracil in propylene glycol on the control side of the face. The experimental side of the face was treated with polypropylene glycol containing 1% fluorouracil and 0.4% triamcinolone acetonide (group 1, n=5), 1% fluorouracil followed by 0.5% triamcinolone acetonide cream (group 2, n=5), or 1% fluorouracil followed by 0.1% triamcinolone cream (group 3, n=5). The inflammatory response evident on the sides of the faces treated with fluorouracil alone was noticeably suppressed in patients treated with fluorouracil in combi-

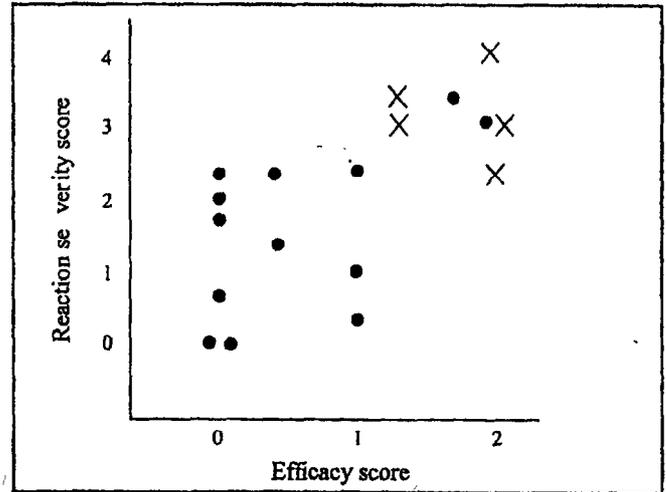


Figure 1: Plot of effectiveness versus reaction severity in 13 patients treated with pulse 5-fluorouracil (Σ) and 5 patients treated with conventional daily 5-fluorouracil (x). Efficacy score: 0=no significant difference; 1=a clearly visible difference; 2=a striking difference. Reaction severity score: 0=normal or slight redness; 1=definite erythema, no erosions, cosmetically acceptable; 2=marked erythema, some erosions, borderline tolerability; 3=marked erosions, not acceptable by any patient; 4=severe reaction with crusting, exudation, and edema²⁸.

nation with 0.4% or 0.5% triamcinolone acetonide cream (groups 1 and 2). In addition, patients preferred combination treatment over treatment with fluorouracil alone, with 6 of the 10 patients in groups 1 and 2 experiencing less burning and 7 of the 10 patients experiencing less crusting and discomfort on the sides of the faces treated with the combination. Interestingly, there were no treatment differences (fluorouracil monotherapy vs. combination therapy) for up to 1 year in the reduction of AK lesions or the appearance of new AK lesions, suggesting that efficacy is not related to degree of inflammation.

Recently, a 0.5% fluorouracil cream formulation that incorporates a microsphere (Microsponge[®]) vehicle has been approved by the Food and Drug Administration for the treatment of AK (Carac[™], Dermik Laboratories, Berwyn, PA). A series of studies have established that this formulation effectively treats AK lesions and has a tolerable irritation profile that is preferred by patients³⁰.

Two identically designed, randomized, double-blind, parallel-group phase III studies evaluated the efficacy and safety of 0.5% fluorouracil cream in a total of 384 patients with AK³⁰. Patients in both studies were randomized to receive 0.5% fluorouracil cream or vehicle control applied once daily to affected areas of the face and scalp for 1, 2, or 4 weeks. Patients were evaluated weekly during the treatment phases as well as during a 4-week post-treatment phase. Efficacy variables included (1) reduction in AK lesions from baseline to the final visit and (2) total lesion clearance as determined by Physician Global Assessment of Improvement (PGAI) scores (-4="much worse" to +5="cured/total clearance"). Paired comparisons were performed between treatment groups.

Table I. Efficacy of microsphere-based 0.5% fluorouracil cream applied once daily.

	0.5% FLUOROURACIL						VEHICLE	
	1-Week		2-Week		4-Week		Study 1	Study 2
	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2		
Reduction from baseline in AK count	69.5*	78.5*	86.1*	83.6*	91.7*	88.7*	21.6	34.4
% of patients with total clearance	14.9*	26.3*	37.0*	19.5†	57.8*	47.5*	0	3.4
PGA overall score	2.3*	3.1*	3.6*	3.2*	4.0*	3.9*	0.5	0.9

*P<.001 vs vehicle.
 †P<.010 vs vehicle.
 AK=actinic keratosis; PGA=Physician Global Assessment of Improvement (ranged from -4=much worse to +5=total clearance).

In both studies, 0.5% fluorouracil cream demonstrated superior efficacy compared with vehicle control^{29,30}. Significant therapeutic effects were observed after only 1 week of treatment^{29,30}. In both studies, proportional reductions from baseline in AK lesions ranged from 69.5% to 78.5%, 83.6% to 86.1%, and 88.7% to 91.7% in the 1-, 2-, and 4-week 0.5% fluorouracil groups, respectively, compared with 21.6% to 34.4% in the vehicle control group (P<.001 for each comparison, both studies; Table I). Furthermore, the proportion of patients with total lesion clearance was significantly greater in all active treatment groups compared with vehicle control (P<.010 for each comparison, both studies) and approached 60% in one of the 4-week active treatment groups. At the final evaluation, patients in the 1-, 2-, and 4-week 0.5% fluorouracil groups also demonstrated significantly greater improvements in PGA scores compared with patients in the vehicle control groups (P<.001 for each comparison, both studies; Table I)^{29,30}.

Facial irritation, which was mild to moderate in severity and occurred in most patients in both the active and vehicle groups, was the most common adverse event in both studies. A plateau of facial irritation was apparent between 2 and 3 weeks of treatment with 0.5% fluorouracil cream. Furthermore, the severity of facial irritation experienced by patients in the 4-week treatment groups was similar to that of the 2-week treatment groups (Fig 2). In both studies, facial irritation resolved to below baseline levels within 2 weeks of treatment cessation. Overall, patients tolerated treatment well in the 2 studies; only 7 of 384 patients discontinued due to adverse events.

Collectively, the 2 phase III studies demonstrate that treatment with 0.5% fluorouracil cream for 1, 2, or 4 weeks effectively reduces AK lesions while maintaining a tolerable irritation profile. The efficacy of the 4-week treatment groups was higher than that of the 2-week treatment groups; however, facial irritation was similar. These findings suggest healing of irritation can occur even with continued treatment, which appears to

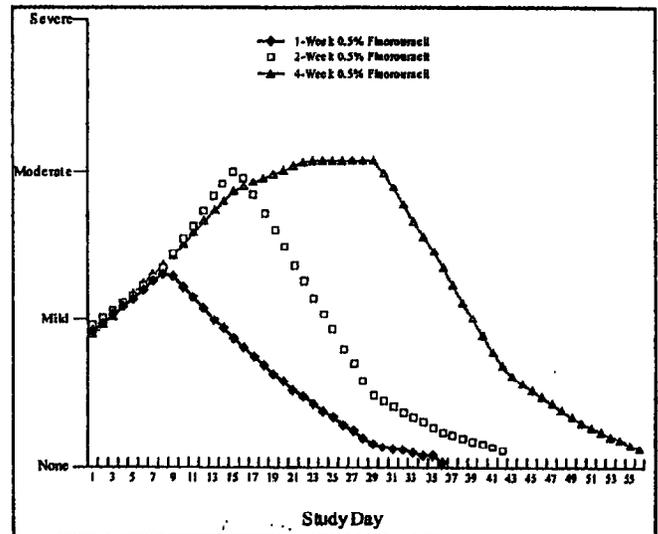


Figure 2: Facial irritation profile from one of the phase III studies²⁹.

enhance efficacy. Therefore, increased irritation may not be necessary to achieve increased efficacy. These findings raise the speculation that perhaps concomitant topical corticosteroids could further reduce facial irritation associated with treatment, without sacrificing effectiveness.

Tolerability and Efficacy of Microsphere-Based Fluorouracil Cream Versus a 5% Fluorouracil Cream

The comparative efficacy of fluorouracil creams of varying strengths in a microsphere base for the treatment of AK was explored in a dose-ranging study that included a vehicle control and a commercially available comparator cream containing 5% fluorouracil (Efudex®). In this double-blind, parallel-group study, 104 patients were randomly assigned to microsphere-

based 0.5%, 2.5%, or 5% fluorouracil cream, vehicle, or comparator 5% fluorouracil cream for 4 weeks twice daily. Patients were followed for an additional 4 weeks post-treatment. Efficacy was primarily determined by treatment group contrasts for reductions in AK lesions and changes in PGAI scores from baseline to final visit.

Treatment with all of the microsphere-based fluorouracil creams significantly ($P < .001$) reduced AK lesions from baseline to final visit compared with vehicle control. There were no statistically significant differences among the microsphere-based fluorouracil cream doses or between these formulations and the comparator 5% cream (Fig 3). All microsphere-based formulations were significantly ($P < .001$) more effective than vehicle in achieving 100% clearance of AK lesions (Fig 3). Once again, there were no significant differences among any of the microsphere cream doses or between any of these doses and the comparator 5% cream for the latter efficacy variable.

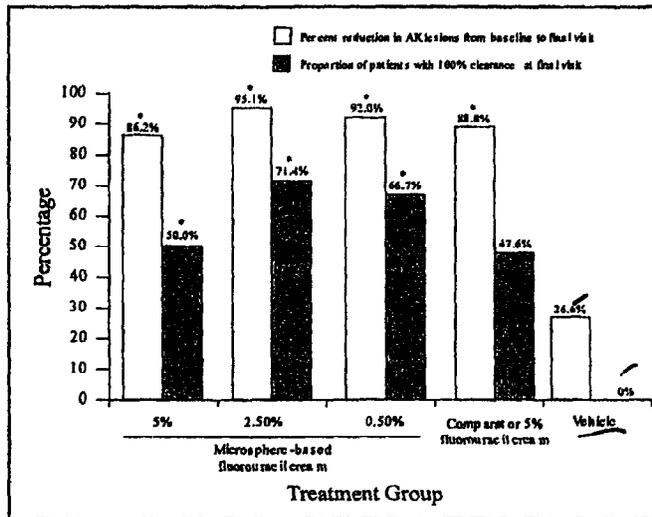


Figure 3: Efficacy of microsphere-based fluorouracil creams compared with a comparator fluorouracil cream and vehicle. $P < .001$ vs. vehicle.

AT 2x wk. Microsphere .56 same as previous 1x wk

Physician-rated facial irritation increased with increasing microsphere-based doses; however, irritation either plateaued or decreased following 2 weeks of treatment in these groups (Fig 4A). In contrast, facial irritation plateaued following 3 weeks of treatment in the comparator 5% cream group but was significantly ($P < .05$) worse at both 3 and 4 weeks compared with the 0.5% and 2.5% fluorouracil groups. At week 2 post-treatment, facial irritation scores declined substantially and appeared similar to that of the vehicle group (Fig 4B).

Separately, a treatment-time response study was conducted to identify the optimal dosing schedule for the microsphere-based 0.5% fluorouracil formulation. A total of 79 patients with AK were randomized to treatment with 0.5% fluorouracil cream administered for 1 week, once daily; 1 week, twice daily; 2 weeks, twice daily; comparator 5% fluorouracil cream, administered for 2 weeks twice daily; or vehicle control. Clinical evaluation was performed twice weekly during the treatment phase and once weekly during a 4-week post-treatment phase. Efficacy was primarily evaluated as percent reduction from baseline in AK lesions and percentage of patients achieving 100% clearance of AK lesions as measured by the PGAI.

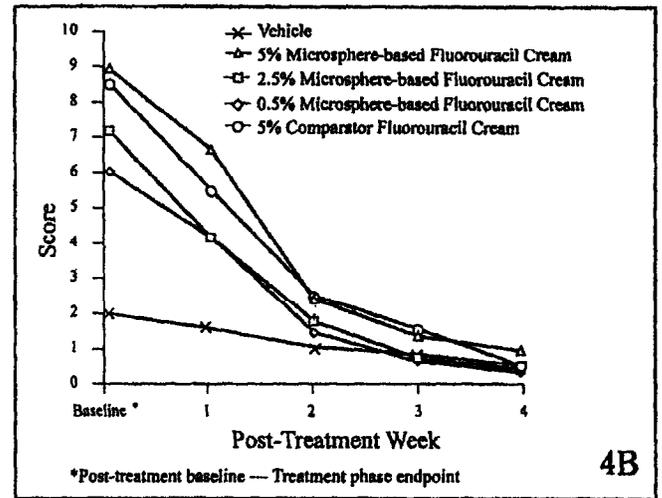
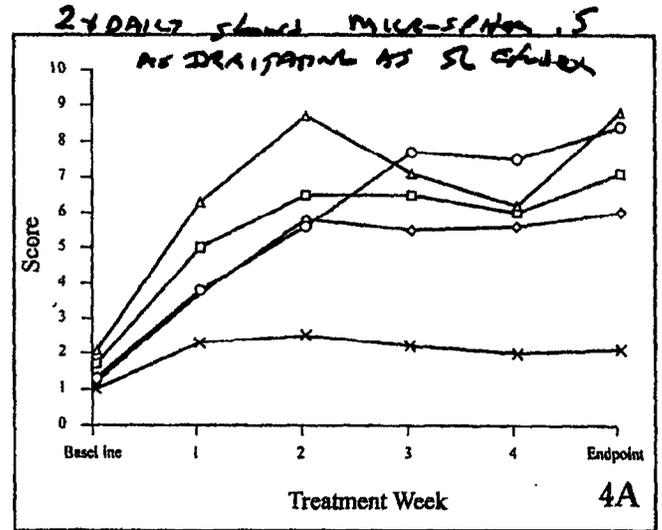


Figure 4: Physician-rated facial irritation scores during (A) treatment phase and (B) post-treatment phase. Score is the sum of 4 components: erythema, dryness, edema, and erosion. Each component was rated on a 4-point scale where 0=none and 3=severe.

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All 0.5% fluorouracil treatment regimens were significantly more effective than vehicle at reducing the percentages of AK lesions ($P < .001$). In addition, significantly ($P < .05$) more patients in the 0.5% fluorouracil cream, twice-daily/2-week treatment group achieved total lesion clearance compared with patients in the vehicle group. Moreover, the efficacy of each 0.5% fluorouracil regimen was not significantly different from that of the comparator 5% fluorouracil regimen for both reduction in AK lesions and percentage of patients with total clearance. Facial irritation measured by the physician declined immediately after treatment cessation (Fig 5A and 5B).

NO DIFFERENCE IN EFFICACY
NO SIDE IN IRRITATION

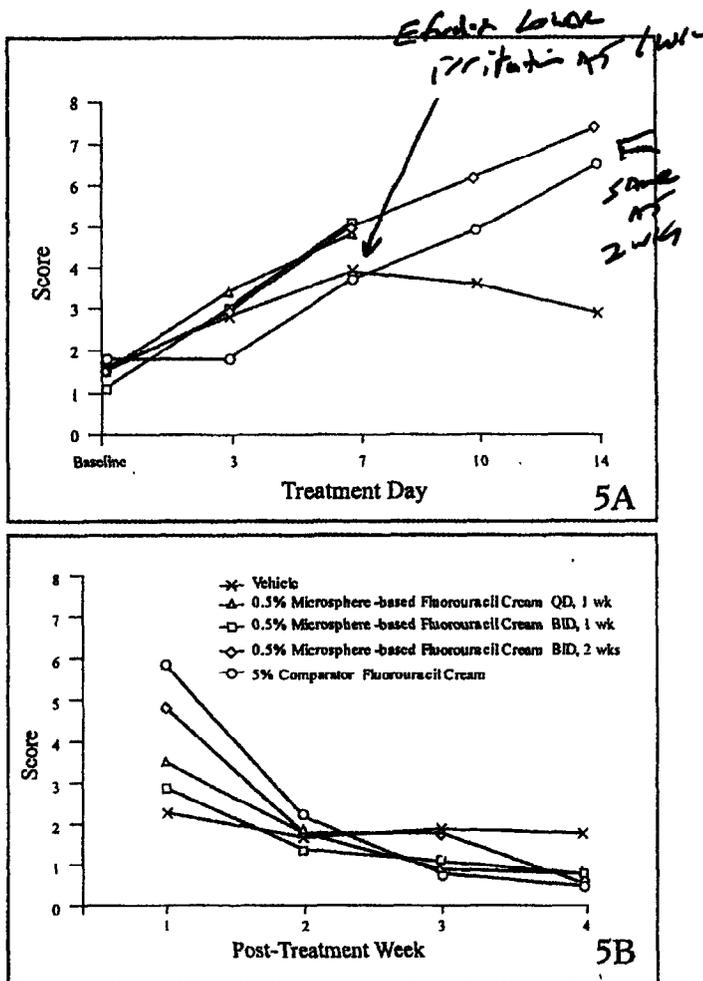


Figure 5: Physician-rated facial irritation scores during (A) treatment phase and (B) post-treatment phase. Score is the sum of 4 components: erythema, dryness, edema, and erosion. Each component was rated on a 4-point scale where 0=none and 3=severe.

Overall, results from the phase II comparative studies indicate that the microsphere-based 0.5% fluorouracil cream is as efficacious as the comparator 5% fluorouracil cream at one tenth of the dose. In addition, the 0.5% formulation appears to have a better tolerability profile, again suggesting that irritation is not always associated with efficacy.

Systemic Tolerability of 5-Fluorouracil Preparations

In addition to disparities in facial irritation and phototoxicity, the systemic absorption of topical formulations of fluorouracil varies, and is affected by the concentration of fluorouracil and the delivery system used. Products containing lower concentrations of the agent may potentially produce less systemic exposure than preparations containing higher concentrations²¹. In addition, microsphere-based delivery systems may minimize systemic toxicity by ensuring that the delivered fluorouracil

remains at the target site²². Permeation and pharmacokinetic studies have confirmed that a greater amount of active ingredient in the microsphere-based 0.5% fluorouracil cream is retained in the skin compared with a comparator 5% fluorouracil cream and that less drug reaches the systemic circulation²³.

A recent in vitro study compared the flux, retention, and percutaneous absorption of fluorouracil from 3 formulations of microsphere-based 0.5% fluorouracil cream with a comparator 5% fluorouracil cream²⁴. Penetration of the 5% fluorouracil cream through skin was 20 to 40 times greater (normalized, 2 to 4 times) than that of the 0.5% formulations (P<.001), with quantitatively less drug retained in the skin following application of the 5% formulation. After 24 hours, a significantly higher percentage of absorbed fluorouracil (86%-92%) remained in the skin following application of the 0.5% formulations compared with the 5% formulation (54%; P<.001), suggesting that the 0.5% formulations have a more targeted delivery (i.e., greater retention of drug in the skin) and hence less potential for systemic exposure.

The pharmacokinetics and tolerability of fluorouracil formulations were investigated in a recent open-label, parallel-group study in which 21 patients with AK were randomized to either microsphere-based 0.5% fluorouracil cream applied once daily or comparator 5% fluorouracil cream applied twice daily for up to 4 weeks²⁵. Despite the 10-fold difference in drug concentration between formulations, the mean cumulative amount of fluorouracil excreted in the urine (i.e., systemic exposure) of patients receiving 0.5% fluorouracil cream was more than 40 times lower than in those receiving the 5% formulation (119.8 vs 2.7 mg, respectively)²⁶, representing 0.55% and 2.4% of the applied doses, respectively²⁷.

Evaluation of facial irritation throughout the study demonstrated that the 0.5% formulation was better tolerated than the 5% formulation²⁸. A lower percentage of patients in the 0.5% fluorouracil cream group experienced moderate facial irritation, and fewer patients discontinued treatment, compared with the 5% fluorouracil cream group. In addition, as noted earlier, facial irritation experienced by patients receiving microsphere-based 0.5% fluorouracil cream reached a plateau following 2 weeks of therapy. These results complement findings from the local tolerability studies and suggest that microsphere-based 0.5% fluorouracil cream is better tolerated and is associated with less flux through the skin than the 5% formulation, which results in minimal systemic absorption (and a lower potential for systemic toxicities), even after repeated topical administration.

Conclusion

AK represents the initial manifestation of a continuum of clinical, histologic, and molecular abnormalities that can progress to invasive SCC. Although topical fluorouracil is effective in treating AK, conventional formulations are associated with sig-

nificant facial irritation that can lead to reduced compliance and limited efficacy. Various efforts have been made to reduce irritation side effects, including alteration of dosing schedules and use of combination therapies. A low-dose, microsphere-based formulation of 0.5% fluorouracil is now available, which appears to be associated with less facial irritation than conventional fluorouracil preparations, without sacrificing effectiveness. The combination of a low-dose formulation and microsphere-based drug-delivery technology may contribute toward improved efficacy, tolerability, and compliance in the large and growing number of patients with AK.

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