NDA 16-831/S-008

JUN 28 1976

Hoffmann-La Roche, Incorporated
Attention: Donald C. Carlton, M.D.
Nutley, New Jersey 07110

Gentlemen:

We acknowledge the receipt on April 13, 1976, of your communication dated April 6, 1976, enclosing printed labeling pursuant to your supplemental new drug application dated September 15, 1972 for Efudex (fluorouracil) Cream, 5% and Solution, 2% and 5%.

The supplemental application as amended provides for a new indication: treatment of superficial basal cell carcinomas (5% strengths only) and other minor labeling revisions.

We have completed the review of this supplemental application, and it is approved. Our letter of July 29, 1970, detailed the conditions relating to the approval of this application.

Sincerely yours,

Marion J. Finkel, M.D.
Associate Director for
New Drug Evaluation
Bureau of Drugs

cc: NWK-DO
NDA Orig.
HFD-100
HFD-616
HFL-10
HFD-140
HFD-140/CSO
HFD-140/JBSanders
HFD-140/DCBostwick/tm/5/27/76

APPROVAL

NDA 16-331/S-008

MAR 1 1 1976

Hoffmann-La Roche, Incorporated
Attention: H. J. Schiffrin, Ph.D.
Nutley, New Jersey 07110

Gentlemen:

We acknowledge the receipt on December 15, 1975, of your communication dated December 11, 1975, regarding your supplemental new drug application of September 15, 1972, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Efudex (fluorouracil) Cream and Solution.

The supplemental application provides for a new indication: treatment of superficial basal cell carcinomas.

We have completed our review of your proposed labeling, and find that the revised INDICATION section is now satisfactory.

Please submit twelve copies of the final printed package insert promptly.

Sincerely yours,

Marion J. Finkel, M.D.
Associate Director
for New Drug Evaluation
Bureau of Drugs

cc: NWK-DO
Orig. NDA
HFD-100
HFD-140
HFD-T40/CSO
JBSanders, M.D.
HLGibson, M.D.
DCBostwick/ep/2/6/76

January 13, 1976

MEDICAL OFFICER'S REVIEW OF NDA 16-831/S -008
Supplemental Correspondance

Sponsor: Hoffman-La Roche, Inc.
Nutley, New Jersey

Product: Efudex cream and solution

Date of Submission: December 11, 1975

I. Introduction and Comment:

A meeting was held on December 11, 1975 with Dr. Donald Carlton of Hoffman-La Roche. At this time the proposed indications for the drug products were discussed and there was mutual agreement in the proposed wording, i.e., the indication section remains essentially the same as that proposed in our approval letter to the sponsor of June 30, 1975, except the addition of the sentence, "With isolated, easily accessible lesions, conventional techniques are preferred, since success with such lesions is almost 100% with these methods". This sentence follows the sentence starting with the words, "The diagnosis should be established", etc. And preceeding the sentence starting with the words, "The success rate with Efudex," etc.

II. Recommendation:

I feel that the package insert labeling with the revision submitted on December 11, 1975 should be approved.

/S/

John B. Sanders, M.D.

cc:
Orig NDA
HFD-108
HFD-140
HFD-140/CSO
HFD-140/JBSanders:llb-1/27/76

May 12, 1976

MEDICAL OFFICER'S REVIEW OF NDA 16-831/S-008
Supplemental correspondance

Sponsor: Hoffmann-La Roche, Inc.
Nutley, New Jersey

Product: Efudex cream and solution.

Date of Submission: April 6, 1976.

Review: This submission contains 12 copies of the final printed package insert labeling for the above named products. The new package insert labeling #13-06-72627-0476 contains 3 changes recommended in our letter of March 11, 1976 (Indications) August 26, 1975 (Adverse reactions) and June 30, 1975 (Dosage and Administration). In reviewing this new package insert all of the changes appear to agree with those proposed.

Recommendation: I feel that the final printed package insert labeling should be approved.

/S/

J. B. Sanders, M.D.

cc:
ORIG. NDA
HFD-140
HFD-140/CSO
HFD-140/JBSanders:abc/05/13/76

January 6, 1975

Medical Officer's Review of Supplement to NDA 16-831

Sponsor: Hoffmann-La Roche, Inc.
Nutley, New Jersey

Product: Efudex 5% Topical Solution
Efudex 5% Topical Cream

Date of Submission: Original - September 15, 1972, Amendment - July 18, 1974.

Reason for Submission: Labeling revision.

I. Description and Summary

The products are presently available in the 5% concentration for both cream and solution plus a 2% concentration for the solution. They are presently indicated for the treatment of multiple senile and/or actinic keratoses. The present submission is to add superficial basal carcinoma (epithelioma) to the indications section of the package insert labeling.

When the submission was last reviewed on March 19, 1973, the application was called "not approvable" because of an insufficient number of case reports derived from well controlled studies. Specifically there was an absence of a sufficient number of pre and post treatment pathology reports, a sufficent number of lesions were not followed for a one year period, some pathology reports disagreed with the clinical diagnosis and finally an occasional biopsy removed the entire lesion, thus not permitting treatment with the drug.

II. Pharmacology:

The product is approved for marketing and this new indication does not involve changes in presently prescribed dosage, etc.

III. Controls:

Not required for this new indication.

IV. Clinical Studies:

Essentially no new patients have been added to those of the original submission, however more data has been provided as requested in our letter of April 17, 1973, as noted in the above comments under "Description and Summary". Thus, the sponsor presents complete data on a total of 113

treatments of which 105 were successful and 8 were considered as failures or a "cure rate" of 93%.

The following table summarizes the results of eight investigators:

Arnold Gould, M.D.
Frederick Mohs, M.D.
Ashbel C. Williams, M.D.
Roy T. Forsberg, M.D.
Edmund Klein, M.D.
Martin S. Litwin, M.D.
E. William Rosenberg, M.D.
Robert D. Sullivan, M.D.

	Superficial Basal Cell Epitheliomas			
	Open		Occluded	
	Cures	Failures	Cures	Failures
Solution 5% Fluorouracil	22	1	2	0
Cream 5% Fluorouracil	54	6	27	1

V. Evaluation and Comment:

1. As noted in our meeting with the sponsor and two investigators (Drs. Klein and Litwin) on April 24, 1974, there are several advantages in the use of topical 5-Fluorouracil in the treatment of superficial basal cell carcinomata;

   a. Treatment of multiple lesions.
   b. Superior cosmetic effect.
   c. Lower cost to the patient.
   d. Facility of treatment in such difficult areas such as; paranasal, angle of mouth and canthus, etc.

2. However, topical chemotherapy should not be considered as the treatment of choice for a solitary superficial basal cell carcinoma! The cure rate for conventional surgical techniques approaches 99-100% as compared to approximately 93% for topical chemotherapy. Furthermore, removal of the lesion by surgical means allows for histopathologic examination and confirmation of the clinical diagnosis.

3. In light of the above comment, the package insert, under the indications section should state: "Efudex is recommended for the topical treatment of multiple actinic and/or solar keratoses. In the 5% strength it may be useful in the management of multiple superficial basal cell carcinomas

4. I feel that the above statement is supported by numerous scientific papers appearing in the dermatologic literature concerning the use of 5-FU in the management of superficial basal cell carcinomas. It is also supporative by carefully controlled studies in the treatment of 113 lesions.

IV. Recommendations:

I feel that there is now adequate documentation and proof presented to support the labeling change as indicated above.

/S/

John B. Sanders, M.D.
Division of Anti-Infective Drug Products

cc:
Orig NDA
Dup NDA
Trip NDA
HFD-100
HFD-140 /S/ 12/7/75
HFD-140/CSO
HFD-140/JBSanders:js
1/28/75

NOV 13 1975

NDA 16-831/S-008

Hoffmann-La Roche, Inc.
Attention: Donald C. Carlton, M.D.
Nutley, New Jersey 07110

Gentlemen:

We acknowledge the receipt on September 22, 1975, of your communication dated September 17, 1975, regarding your supplemental new drug application of September 15, 1972, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Efudex (fluorouracil) Cream and Solution.

The supplemental application provides for a new indication: treatment of superficial basal cell carcinomas.

We have completed our review of your proposed labeling, and find that the Indications section recommended in our June 30, 1975 letter should be implemented unchanged. It is our opinion that the physician should be fully aware of the difference in effectiveness between conventional methods and treatment with Efudex for this indication.

Please submit labeling revised as recommended in our June 30, 1975 and August 26, 1975 letters concerning this product.

Sincerely yours,

Marion J. Finkel, M.D.
Acting Associate Director
for New Drug Evaluation
Bureau of Drugs

cc: NWK-DO
HFD-100/Dr. Finkel
HFD-140
HFD-140/CSO
DCBostwick/HFD-140
HFD-140/JBSanders/10/20/75/cg/10/24/75
R/D init by: MLGibson/10/23/75

NDA 15-831/S-030

JUN 30 1975

Hoffmann-La Roche, Inc.
Attention: Donald C. Carlton, M.D.
Nutley, New Jersey 07110

Gentlemen:

Reference is made to your supplemental new drug application of September 15, 1972, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Efudex (fluorouracil) Cream and Solution.

We also acknowledge receipt of your additional communications dated September 18, 1973, July 18, 1974, and February 18, 1975.

The supplemental application provides for a new indication: treatment of superficial basal cell carcinomas.

We have completed the review of this supplemental application as submitted with draft labeling. However, before this supplement may be approved, it will be necessary for you to submit final printed labeling. The labeling should be identical in content to the draft copy except for the following revisions:

1. The INDICATIONS section should read: "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. The diagnosis should be established prior to treatment since this new method has not been proven effective in other types of basal cell carcinomas. The success rate when using Efudex cream and solution is approximately 93% compared to almost 100% when conventional techniques are used. The 93% success rate is based on 113 lesions in 54 patients. Twenty-five lesions treated with the solution produced one failure and 90 lesions treated with the cream produced 7 failures."

2. Under the sub-section on superficial basal cell carcinoma in the DOSAGE AND ADMINISTRATION section, the following sentence should be included:

> As in any neoplastic condition, the patient should be followed for a reasonable period of time to determine if a cure has been obtained.

Please submit twelve copies of the printed labeling promptly.

Sincerely yours,

J. Richard Crout, M.D.
Director
Bureau of Drugs

cc: HMK-DO
Orig. NDA
HFD-1
HFD-140
HFD-140/CSO
HFL-10
JESanders/HFD-140
MLGibson/HFD-140
HFD-140/DCBostwick/5-13-75/cg/5-12-75/5-20-75/6-3-75
N/S init by: MLGibson/5-8-75/5-14-75/5-30-75
PGWalters/5-15-75

APPROVABLE

December 11, 1975

MEMORANDUM OF MEETING

Present: Donald Carlton, M.D.
Hoffmann-LaRoche

and

M. L. Gibson, M.D.
J. B. Sanders, M.D.
HFD-140

Subject: Efudex, NDA 16-831, Proposed New Indication, Package Insert Labeling.

Dr. Carlton stopped by to briefly discuss a change that the company desires in the proposed package insert labeling for Efudex. In essence the indication would remain the same except to add a new sentence i.e., "with isolated, easily accessible lesions, conventional techniques are preferred since success with such lesions is almost 100% with these methods". The sentence would follow the sentence starting with the words, "The diagnosis should be established, "etc. and would preceed the sentence starting with the words, "The success rate with Efudex," etc.

There was agreement indicated to this change and Dr. Carlton was informed that it would be forwarded to higher authority for approval.

J. B. Sanders, M.D.

cc:
HFD-140
HFD-108
JBSanders/vha/12/16/75

NDA 16-831/S-008
Efudex (fluorouracil) Cream and Solution
Hoffmann-LaRoche, Inc.

DIVISION DIRECTOR'S SUMMARY

This product is presently marketed for the treatment of multiple solar and/or actinic keratoses. It has been used for superficial basal cell carcinomas for some time by the medical profession without approved labeling. The sponsor submitted a supplement on September 15, 1972 for this indication. An approvable letter issued June 30, 1975, which included a recommended Indications section mentioning cure rates and failures. The sponsor does not wish to include the cure rates and failures in his labeling.

The Medical officer review finds that there is no good reason for not including this information. We feel that knowledge of the difference in effectiveness between conventional methods of therapy and Efudex for this infication are essential to the practicing physician. We are therefore recommending that the June 30, 1975 Indications section sent to the sponsor be implemented unchanged.

Merle L. Gibson, M.D.
Director
Division of Anti-Infective
Drug Products
Office of New Drug Evaluation
Bureau of Drugs

cc:
ORIG. NDA
HFD-140
HFD-140/DCBostwick:abc/10/25/75
HFD-140/MLGibson 10/23/75