

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-155/S-019 & S-020

Trade Name: Lac-Hydrin Lotion, 12%

Generic Name: ammonium lactate

Sponsor: Bristol-Myers Squibb Company

Approval Date: April 4, 2004

Indication: Treatment of dry, scaly skin (xerosis) and ichthyosis vulgaris and for temporary relief of itching associated with these conditions.

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APPLICATION NUMBER:
19-155/S-019 & S-020

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APPLICATION NUMBER:
19-155/S-019 & S-020

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-155/S-019 & S-020

Bristol-Myers Squibb Company
Attention: David L. Silberstein
Associate Director, RDP&M
PO Box 4000
Princeton, NJ 08543-4000

Dear Mr. Silberstein:

Please refer to your supplemental new drug applications dated August 24, 2000 and January 24, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lac-Hydrin (ammonium lactate) Lotion, 12%.

These supplemental new drug applications provide for labeling changes to parallel the changes recently approved for Lac-Hydrin Cream, and incorporation of other minor editorial revisions.

Your submission of December 19, 2003, constituted a complete response to our May 28, 2003 action letter.

We completed our review of these supplemental new drug applications as amended, and they are approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted. At the next printing, please make the following change in the labeling for LacHydrin: the percentage of strength should follow the dosage form preceded by a comma (LacHydrin (ammonium lactate) Lotion, 12%).

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Stanka Kukich
4/28/04 06:06:12 PM
Sign off for Dr. Wilkin

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
19-155/S-019 & S-020

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-155/S-020

Westwood-Squibb Pharmaceuticals, Inc.
Attention: David L. Silberstein
Associate Director, Regulatory Science
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Silberstein:

Please refer to your supplemental new drug application dated January 24, 2001, received January 29, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lac-Hydrin[®] (ammonium lactate lotion) Lotion, 12%.

This supplemental new drug application provides revised labeling revised to parallel the labeling approved on August 25, 2000 for NDA 20-508/S-005 Lac-Hydrin[®] (ammonium lactate cream) Cream, 12%, and to incorporate other minor editorial revisions to the DESCRIPTION section and the corporate address.

This supplemental application was reviewed as a prior approval supplement as you requested on April 25, 2003 in a telephone communication with Leslie Vaccari.

We completed our review of this application and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for this drug. The labeling should be identical in content to the submitted labeling (package insert) submitted January 24, 2001. In addition, all previous revisions as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

Please submit 20 paper copies of the FPL, 10 of which are mounted individually on heavy-weight paper or similar material. Alternately, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be necessary.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such an action, FDA may proceed to withdraw this application. Any amendment should respond to the request listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.

Director

Division of Dermatologic & Dental Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

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/s/

John Kelsey
5/28/03 04:36:33 PM
for Dr. Wilkin



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-155/S-019

Westwood-Squibb Pharmaceuticals, Inc.
Attention: David L. Silberstein
Associate Director, Regulatory Science
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Silberstein:

Please refer to your supplemental new drug application dated August 24, 2000, received August 29, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lac-Hydrin[®] (ammonium lactate lotion) Lotion, 12%.

This supplemental new drug application provides for the addition of a Geriatric Use subsection in the PRECAUTIONS section.

We completed our review of this application and it is approvable. Before this application may be approved, however, you must submit final printed labeling revised as follows:

The PRECAUTIONS section, Geriatric Use subsection should read as follows:

Clinical studies of Lac-Hydrin[®] (ammonium lactate lotion) Lotion, 12% did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious.

Please submit 20 paper copies of the FPL. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternately, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA.

In addition, all previous revisions as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

These changes may not be implemented until you have been notified in writing that this supplemental new drug application is approved.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be necessary.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such an action, FDA may proceed to withdraw this application. Any amendment should respond to the request listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.

Director

Division of Dermatologic & Dental Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

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/s/

John Kelsey
5/28/03 04:37:40 PM
for Dr. Wilkin

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
19-155/S-019 & S-020

LABELING

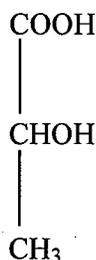
Lac-Hydrin[®] 12%*

(ammonium lactate) Lotion

For Dermatologic use only. Not for Ophthalmic, Oral or Intravaginal use.

DESCRIPTION

*Lac-Hydrin specially formulates 12% lactic acid, neutralized with ammonium hydroxide, as ammonium lactate to provide a lotion pH of 4.5-5.5. Lac-Hydrin[®] 12% (ammonium lactate) Lotion also contains cetyl alcohol, fragrance, glycerin, glyceryl stearate, laureth-4, light mineral oil, magnesium aluminum silicate, methylcellulose, methyl and propyl parabens, PEG-100 stearate, polyoxyl 40 stearate, propylene glycol and water. Lactic acid is a racemic mixture of 2-hydroxypropanoic acid and has the following structural formula:



CLINICAL PHARMACOLOGY

It is generally accepted that the water content of the stratum corneum is a controlling factor in maintaining skin flexibility. When the stratum corneum contains more than 10% water it remains soft and pliable; however, when the water content drops below 10% the stratum corneum becomes less flexible and rough, and may exhibit scaling and cracking and the underlying skin may become irritated.^{1,2}

Symptomatic relief of dry skin is provided by skin protectants containing hygroscopic substances (humectants) which increase skin moisture. Lactic acid, an α -hydroxy acid, is reported to be one of the most effective naturally occurring humectants in the skin.³ The α -hydroxy acids (and their salts), in addition to having beneficial effects on dry skin, have also been shown to reduce excessive epidermal keratinization in patients with hyperkeratotic conditions (e.g., ichthyosis).⁴

Pharmacokinetics

The mechanism of action of topically applied neutralized lactic acid is not yet known.

INDICATIONS AND USAGE

Lac-Hydrin is indicated for the treatment of dry, scaly skin (xerosis) and ichthyosis vulgaris and for temporary relief of itching associated with these conditions.

CONTRAINDICATIONS

Known hypersensitivity to any of the label ingredients.

WARNING

Sun exposure to areas of the skin treated with Lac-Hydrin 12% (ammonium lactate) Lotion should be minimized or avoided (see **PRECAUTIONS** section).

PRECAUTIONS

General

For external use only. Stinging or burning may occur when applied to skin with fissures, erosions or that is otherwise abraded (for example, after shaving the legs). Caution is advised when used on the face because of the potential for irritation. The potential for post-inflammatory hypo- or hyperpigmentation has not been studied.

Information For Patients

Patients using Lac-Hydrin 12% (ammonium lactate) Lotion should receive the following information and instructions:

1. This medication is to be used as directed by the physician, and should not be used for any disorder other than for which it was prescribed. It is for external use only. Avoid contact with eyes, lips, or mucous membranes.
2. Patients should minimize or avoid use of this product on areas of the skin that may be exposed to natural or artificial sunlight, including the face. If sun exposure is unavoidable, clothing should be worn to protect the skin.
3. This medication may cause transient stinging or burning when applied to skin with fissures, erosions, or abrasions (for example after shaving the legs).
4. If the skin condition worsens with treatment, the medication should be promptly discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The topical treatment of CD-1 mice with 12%, 21% or 30% ammonium lactate formulations for two years did not produce a significant increase in dermal or systemic tumors in the absence of increased exposure to ultraviolet radiation. The maximum systemic exposure of the mice in this study was 0.7 times the maximum possible systemic exposure in humans. However, a long-term photocarcinogenicity study in hairless albino mice suggested that topically applied 12% ammonium lactate formulations enhanced the rate of ultraviolet light-induced skin tumor formation.

The mutagenic potential of ammonium lactate formulations was evaluated in the Ames assay and in the mouse *in vivo* micronucleus assay, both of which were negative.

In dermal Segment I and III studies with ammonium lactate formulations there were no effects observed in fertility or pre- or post-natal development parameters in rats at dose levels of 300 mg/kg/day (1800 mg/m²/day), approximately 0.4 times the human topical dose.

Pregnancy

Teratogenic effects: Pregnancy Category B

Animal reproduction studies have been performed in rats and rabbits at doses up to 0.7 and 1.5 times the human dose, respectively (600 mg/kg/day, corresponding to 3600 mg/m²/day in the rat and 7200 mg/m²/day in the rabbit) and have revealed no evidence of impaired fertility or harm to the fetus due to ammonium lactate formulations. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Lac-Hydrin Lotion should be used during pregnancy only if clearly needed.

Nursing Mothers

Although lactic acid is a normal constituent of blood and tissues, it is not known to what extent this drug affects normal lactic acid levels in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lac-Hydrin is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Lac-Hydrin have been demonstrated in infants and children. No unusual toxic effects were reported.

Geriatric Use

Clinical studies of Lac-Hydrin 12% (ammonium lactate) Lotion did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious.

ADVERSE REACTIONS

The most frequent adverse experiences in patients with xerosis are transient stinging (1 in 30 patients), burning (1 in 30 patients), erythema (1 in 50 patients) and peeling (1 in 60 patients). Other adverse reactions which occur less frequently are irritation, eczema, petechiae, dryness and hyperpigmentation.

Due to the more severe initial skin conditions associated with ichthyosis, there was a higher incidence of transient stinging, burning and erythema (each occurring in 1 in 10 patients).

OVERDOSAGE

The oral administration of Lac-Hydrin to rats and mice showed this drug to be practically non-toxic ($LD_{50} > 15$ ml/kg).

DOSAGE AND ADMINISTRATION

Shake well. Apply to the affected areas and rub in thoroughly. Use twice daily or as directed by a physician.

HOW SUPPLIED

Lac-Hydrin[®] 12% (ammonium lactate) Lotion is available in a 225g (NDC 0072-5712-08) plastic bottle and a 400g (NDC 0072-5712-14) plastic bottle.

Store at controlled room temperature 15° C-30° C (59° F-86° F).

REFERENCES

1. Blank IH: Further observation on factors which influence the water content of the stratum corneum. *J Invest Dermatol* 21: 259 - 271, 1953.
2. Blank IH: Factors which influence the water content of the stratum corneum. *J Invest Dermatol* 18: 433 - 440, 1952.
3. Middleton JD: Sodium lactate as a moisturizer. *Cosmetics and Toiletries* 93: 85 - 86, 1978.
4. VanScott EJ and Yu RJ: Modulations of keratinization with α -hydroxy acids and related compounds. In: *Recent Advances in Dermatopharmacology*, P. Frost, E.E. Gomez and N. Zaias (eds) Spectrum Publications, Inc. NY, 211 - 217, 1977.

Bristol-Myers Squibb Co.
Princeton, NJ 08543 USA

53-022709-01
53-022710-01
Revised October 2003

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
19-155/S-019 & S-020

MEDICAL REVIEW

**Medical Officer's Review of Drug Label
Division of Dermatology And Dental Drug Products, HFD - 540**

NDA: 19-155

Document ID Number: SLR-020, SLR-019

HFD 540:

Correspondence date: 01/24/01

CDER stamp date: 01/29/01

Review date: 04/10/03

Applicant: Bristol-Myers Squibb Pharmaceutical Research Institute

Drug: Lac-Hydrin[®] Lotion 12%

Dosage Form and Route of Administration: Topical

Active Ingredient(s): Ammonium Lactate

Pharmacologic Category: Alpha-hydroxy acid

Indication: Treatment of ichthyosis vulgaris and xerosis

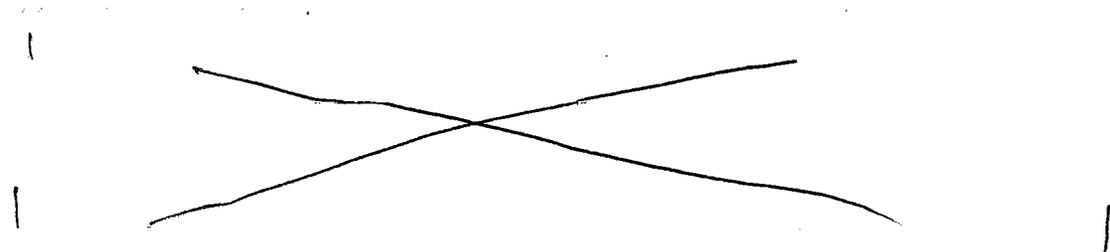
Background:

Lac-Hydrin 12% Lotion was approved April 24, 1985.

Applicant's Proposed Labeling Revisions:

The applicant submitted two labeling supplements, SLR-019 and SLR-020.

1. S-019 (prior approval): Geriatric Use subsection addition supplement, labeling change as follows:



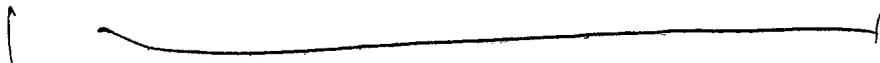
2. S-020 (CBE): Labeling changes to parallel changes approved for NDA 20-508/S-005, Lac-Hydrin Cream approved August 25, 2000.

Reviewer's Comments:

1. S-019 Geriatric Use addition to the PRECAUTIONS section

In response to FDA's final rule published August 27, 1997 regarding the addition of "Geriatric Use" subsection in labeling, the sponsor had sent a submission providing proposed labeling changes to reflect experience with geriatric use of Lac-Hydrin Lotion. The added section notes that no overall differences in safety or effectiveness were observed between elderly and younger patients.

Upon review of the submitted application, about 6% of patients were 60-70 years of age and about 8% of patients were 70-80 years of age. The applicant incorrectly calculated the percent of patients in each age group based on the data provided in the application. In addition, the geriatric labeling supplements generally require patients 65 years and older, also the adverse reaction table does not delineate patients more than 65 years of age. Since this is a small percentage of patients, the Geriatric Use subsection should read as follows:



Recommendation for S-019:

This supplemental application is approvable with the recommended Geriatric Use statement. This change conforms to 21 CFR 201.57(f)(10)(ii)(B).

2. S-020 Labeling changes to parallel changes in NDA 20-508/S-005 Lac-Hydrin Cream
NDA 20-508/S-005 was approved August 25, 2000 providing for the use of Lac-Hydrin Cream for the treatment of ichthyosis vulgaris and xerosis in pediatric patients as young as 2 years of age. In addition, other specific revisions were made to the WARNINGS, and PRECAUTIONS sections of the labeling. Since Lac-Hydrin Cream and Lotion contain the same active ingredient at the same concentration and are qualitatively identical in composition, sponsor believes that the data which supported the changes in labeling for the cream apply equally to the lotion which are proposed in this labeling supplement, S-020.

Proposed changes to Labeling NDA 19-155 Lac-Hydrin 12% (ammonium lactate) Lotion	
Summary of Change	Supporting Rationale
Change "topical use" to "dermatological use" and add "oral or intravaginal use"	Editorial change, to parallel existing cream labeling(NDA 20-508) and other BMS products.
DESCRIPTION: The order of ingredients is revised to list the inactive ingredients in alphabetical order.	Editorial change -Complies with USP guidance on alphabetical listing of inactive ingredients.
WARNING:	Change conforms to revised cream labeling

Proposed changes to Labeling NDA 19-155 Lac-Hydrin 12% (ammonium lactate) Lotion	
PRECAUTIONS : General: deletes the statement to "Avoid contact with mucous membranes"	Redundant, conforms to deletion made to cream labeling in approval of S-005
Carcinogenesis, Mutagenesis, Impairment of Fertility: adds the results of a dermal carcinogenicity study in CD-1 mice	Change incorporates language from revised cream labeling
Pregnancy/ Teratogenic effects : Pregnancy category is changed to B and details on animal reproduction studies are added	Change incorporates entire revised section from cream labeling, including changes in section title, change in pregnancy category and summary of data
HOW SUPPLIED: Fahrenheit storage is added; NSN number is deleted. Section now begins with phrase "Lac-Hydrin 12% (ammonium lactate) Lotion is available in a"	Editorial change parallels style used for most recent version of cream labeling
Address of sponsor and company logo is changed to Bristol-Myers Squibb, Princeton, NJ	Reflects relocation of corporate offices
Changes in typography (fonts, size, capitalization, bolding, etc.)	Editorial changes to conform to common style used for other products of manufacturer

Recommendation for S-020:

The proposed changes as submitted in S-020 are acceptable.

During the review of these supplemental applications, S-019 and S-020, the sun exposure statement in the WARNING and PRECAUTIONS section of the label was also reviewed. This section adequately addresses concerns raised by current FDA/CFSAN guidelines for sun exposure regarding cosmetics (Lac-Hydrin is a drug product and not a cosmetic product) containing alpha hydroxy acid.

This has been discussed with the Pharm/Tox team.

Conclusions:

1. Recommendation for S-019:

This supplemental application for Geriatric use in label change is approvable with the following recommendations:

This proposed change conforms to 21 CFR 201.57(f)(10)(ii)(B).

2. Recommendation for S-020:
The proposed changes as submitted in S-020 are acceptable and the supplement may be approved.
3. The current labeling precautions about sun exposure are acceptable.

If additional information relating to the safety or effectiveness of this drug become available, labeling revision(s) may be required.

Bindi Nikhar, M.D.
Medical Officer

For concurrence:
HFD-540/TL/LukeM
HFD540/DD/WilkinJ
In DFS:

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/s/

Bindi Nikhar
4/30/03 11:08:45 AM
MEDICAL OFFICER

Markham Luke
5/7/03 12:35:27 PM
MEDICAL OFFICER
Labeling review for LacHydrin Lotion. No comments to be
conveyed to Sponsor. Labeling should reflect MO conclusions.

Jonathan Wilkin
5/18/03 02:04:06 PM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-155/S-019 & S-020

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

MEMORANDUM

To: NDA 19-155

Through: Abby Jacobs, Ph.D., Pharm/Tox Team Leader, Division of Dermatologic and Dental Drug Products

From: Paul C. Brown, Ph.D., Pharmacology/Toxicology Reviewer, Division of Dermatologic and Dental Drug Products

Date: April 29, 2003

Re: SLR-015/ 31 March 1997, 24 June 1997, 11 July 1997
SLR-020/ 24 January 2001

Drug: Lac-Hydrin (ammonium lactate cream) Lotion, 12%

Introduction and Discussion:

The applicant submitted a report of a dermal carcinogenicity study and proposed wording describing the study for the label of Lac-Hydrin Cream (NDA 20-508) on October 14, 1996. This report and wording was previously reviewed by Dr. Syed Alam in a review dated March 24, 1997. Dr. Alam found it acceptable to incorporate the wording in the Cream label. On March 31, 1997 the applicant submitted SLR-015 to NDA 19-155, in which they proposed adding a description of a photocarcinogenicity study to the lotion label. On June 17, 1997 the applicant was advised to also incorporate a description of the dermal carcinogenicity study into the lotion label. On January 24, 2001 the applicant submitted SLR-020 to NDA 19-155. This supplement harmonized the wording in the cream and lotion labels. This included adding the same description of the dermal carcinogenicity study to the lotion label that was approved on August 25, 2000 for the cream label. This wording is shown below.

Labeling:

The following wording for the Carcinogenesis, Mutagenesis and Impairment of Fertility section of the label was proposed by the sponsor for the lotion label in SLR-015 and is the same as that approved for the cream label.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The topical treatment of CD-1 mice with 12%, 20% or 30% ammonium lactate formulations for two-years did not produce a significant increase in dermal or systemic tumors in the absence of increased exposure to ultraviolet radiation. The maximum systemic exposure of the mice in this study was 0.7 times the maximum possible systemic exposure in humans. However, a long-term photocarcinogenicity study in hairless albino mice suggested that topically applied 12% ammonium lactate cream enhanced the rate of ultraviolet light-induced skin tumor formation.

The mutagenic potential of ammonium lactate cream was evaluated in the Ames assay and in the mouse *in vivo* micronucleus assay, both of which were negative.

In dermal Segment I and III studies with ammonium lactate cream there were no effects observed in fertility or pre- or post-natal development parameters in rats at dose levels of 300 mg/kg/day (1800 mg/m²/day), approximately 0.4 times the human topical dose.

Conclusions:

The proposed labeling shown above supercedes the wording reviewed in 1997 for the S-015 supplement to this NDA. This labeling was found acceptable in the review of the cream (NDA 20-508/S-005) and is also acceptable for the lotion. The S-015 supplement of NDA 19-155 may be closed from a pharm/tox perspective.

Paul C. Brown, Ph.D.
Pharmacology/Toxicology Reviewer

Abby Jacobs, Ph.D.
Pharmacology/Toxicology Supervisor

cc:
HFD-540/Pharm. Tox. Sup./Jacobs
HFD-540/Div. Dir./Wilkin
HFD-540/PM/Owens
HFD-540/Sup. PM/Kozma-Fornaro
HFD-105/Reg. PM/Vaccari

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/s/

Paul Brown
4/29/03 09:11:58 AM
PHARMACOLOGIST

Abby Jacobs
4/29/03 09:39:53 AM
PHARMACOLOGIST

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APPLICATION NUMBER:
19-155/S-019 & S-020

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Division of Dermatologic & Dental Drug Products
REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 19-155/S-019 and S-020

Name of Drug: Lac-Hydrin (ammonium lactate) Lotion, 12%

Applicant: Bristol-Myers Squibb Pharmaceutical Research Institute.

Material Reviewed:

Final Printed Labeling for NDA 19-155/S-019 and S-020

Submission Date: December 19, 2003

Receipt Date(s): December 23, 2003

Background and Summary

Applicant has submitted FPL in response to FDA May 28, 2003 AE letters. NDA 19-155/S-019 & S-020 submitted on January 24, 2001, received January 29, 2001, provide for revised labeling to parallel the labeling approved on August 25, 2000 for NDA 20-508/S-005, Lac-Hydrin (ammonium lactate cream) Cream, 2%, and to incorporate other minor editorial revisions to the DESCRIPTION Section and the corporate address and the addition of the Geriatric Use labeling requirements under 21 CFR 201.57(f)(10).

An approvable letter was issued on May 28, 2003 with a request for final printed labeling identical to draft labeling submitted by the Applicant on January 24, 2001. The Applicant has submitted FPL in response to our May 28, 2003 Approval Letter.

Review

Comparison of the FPL submitted December 19, 2003 to the labeling submitted by the Applicant on January 24, 2001, and the Geriatric subsection wording requested in our May 28, 2003 Approval Letter.

Description: No changes noted.

Clinical Pharmacology: No changes noted.

Pharmacokinetics: No changes noted

Indications and Usage: No changes noted.
NDA 19-155/S-019 & S-020

Contraindications: No changes noted.

Warning: No changes noted.

Precautions:

General: No changes noted.

Information for Patients: No changes noted.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No changes noted.

Pregnancy: Teratogenic Effects: Pregnancy Category B: No changes noted.

Nursing Mothers: No changes noted.

Pediatric Use: No changes noted.

Geriatric Use: In the first sentence, the product is cited as "Lac-Hydrin 12% (ammonium lactate) Lotion. In FDA's May 28, 2003 letter, it is cited as "Lac-Hydrin (ammonium lactate lotion) Lotion, 12%".

This is acceptable. However, the percentage of strength generally follows the dosage form, preceded by a comma.

Adverse Reactions: No changes noted.

Overdosage: No changes noted.

Dosage and Administration: No changes noted.

How Supplied: The NDC number for the 400 g bottle has been changed from / to "0072-5712-14".

This is acceptable. It seems to be an internal correction.

References: No changes noted.

Conclusions

The Final Printed Labeling is acceptable. An Approval Letter will be issued.

Suzanne Childs
Consumer Safety Technician

Supervisory Comment/Concurrence:

Mary Jean Kozma-Fornaro
Chief, Project Management Staff

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/s/

Suzanne Childs
3/3/04 03:27:49 PM
TECHNICAL

Mary Jean Kozma Fornaro
3/22/04 10:35:45 AM
CSO
FPL to be attached to approval letter

**Division of Dermatologic and Dental Drug Products
HFD-540**

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 19-155/S-015
NDA 19-155/S-019
NDA 19-155/S-020

Name of Drug: Lac-Hydrin[®] (ammonium lactate lotion) Lotion, 12%

Applicant: Bristol-Myers Squibb Company
Attention: David Silberstein
Associate Director, Regulatory Science
P.O. Box 4000
Princeton, New Jersey 08543-4000

Materials Reviewed

NDA/SLR	Submission Date	Receipt Date
1. NDA 19-155/S-015	31 March 1997	07 April 1997
NDA 19-155/S-015BL	24 June 1997	01 July 1997
NDA 19-155/S-015BP	11 July 1997	21 July 1997
2. NDA 19-155/S-019	24 August 2000	29 August 2000
3. NDA 19-155/S-020	24 January 2001	29 January 2001

Background and Summary

1. NDA 19-155/S-0015 submitted on March 31, 1997, received April 7, 1997 provides for the addition of a statement to the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection, supported by the dermal carcinogenicity study as follows:

} _____

The amendment to S-015 dated June 24, 1997 and received July 1, 1997 provides a complete response to all FDA questions detailed in FDA facsimile dated June 17, 1997.

The amendment to S-015 dated July 11, 1997 and received July 21, 1997, provides a complete response to the FDA facsimile dated June 5, 1997, and to the teleconference with Dr. S. Alam on July 10, 1997 when requests were made for additional information.

2. NDA 19-155/S-019 submitted on August 24, 2000, received on August 29, 2000, provides for the addition of Geriatric Use subsection to the PRECAUTIONS section of the labeling.

This supplemental application addresses Geriatric Use labeling requirements under 21 CFR 201.57(f)(10) as follows:



3. NDA 19-155/S-020 identified as a special supplement changes being effected submitted on January 24, 2001, received on January 29, 2001, provides revised labeling changed to parallel the labeling approved on August 25, 2000 for NDA 20-508/S-005 Lac-Hydrin[®] (ammonium lactate cream) Cream 12% and to incorporate other minor editorial revisions to harmonize the DESCRIPTION section and corporate address used in the labeling of the two products.

On April 25, 2003, during a telecon between David Silberstein of Bristol-Myers Squibb and Leslie Vaccari, Mr. Silberstein stated that this supplemental application is not a special supplement changes being effected and should be classified as a prior-approval supplement.

Review

NDA 19-155/S-015

Pharmacology Review

The proposed labeling revision in S-015 is identical to the labeling proposed in NDA 20-508/~~005~~ which was reviewed at the same time as NDA 20-508/S-005. On August 25, 2000, NDA 20-508/S-005 was approved for the treatment of ichthyosis vulgaris and xerosis in pediatric patients as young as 2 years old. The revised labeling also included the addition of a statement to the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection, supported by the dermal carcinogenicity study as follows:

The topical treatment of CD-1 mice with 12%, 21% or 30% ammonium lactate formulations for two-years did not produce a significant increase in dermal or systemic tumors in the absence of increased exposure to ultraviolet radiation. The maximum systemic exposure of the mice in this study was 0.7 times the maximum possible systemic exposure in humans.

NDA 19-155/S-020 provides revised labeling changed to parallel the labeling approved on August 25, 2000 for NDA 20-508/S-005 Lac-Hydrin[®] (ammonium lactate cream) Cream 12%. Therefore, the labeling changes that include the statement on the carcinogenicity study results have been approved in NDA 20-508/S-005 and submitted as proposed labeling in NDA 19-155/S-020. At this time, S-015 has been superceded by S-020 that will be approved.

NDA 19-155/S-019

Medical Officer Review

The review of NDA 19-155/S-019 was completed by the Medical Officer. See the review of NDA 19-155/S-019 in DFS. Adequate data was not submitted for the proposed alternative statement as provided under 21 CFR 201.57(f)(10)(ii)(B); therefore, it was recommended that the applicant comply with 21 CFR 201.57(f)(10)(ii)(A) in the PRECAUTIONS: Geriatric Use section of the label to read:

Clinical studies of Lac-Hydrin® (ammonium lactate lotion) Lotion, 12% did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious.

The supplemental application is approvable with the proposed FDA wording.

NDA 19-155/S-020

Medical Officer Review

The review of NDA 19-155/S-020 was completed by the Medical Officer. See the review of NDA 19-155/S-020 in DFS. The application is acceptable and is approvable.

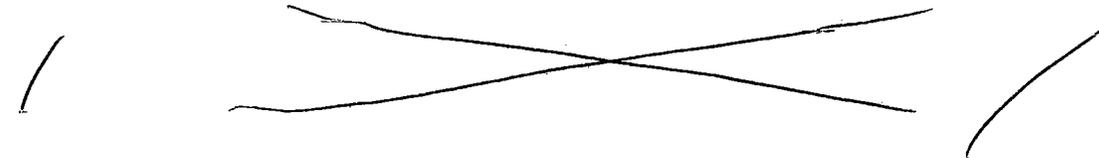
NDA 19-155

Project Manager Review

No other labeling supplements or final printed labeling have been submitted to NDA 19-155 except for those identified.

During the regulatory review of S-020, it was noted that not all of the proposed labeling sections were consistent with the Lac-Hydrin Cream label approved with NDA 20-508/S-005. The differences are as follows.

1. The CLINICAL PHARMACOLOGY section contains general information based on literature dating between 1952 and 1978.



Reviewer's recommendation:

2. The CONTRAINDICATIONS section for the lotion contains the statement "Known hypersensitivity to any of the label ingredients." The Lac-Hydrin Cream label says "None

known.”

Reviewer's recommendation:

- 3. The WARNING section in the Lac-Hydrin Lotion label reads “Sun exposure to areas of the skin treated with Lac-Hydrin Lotion should be minimized or avoided (see PRECAUTIONS section).” which is not consistent with the Lac-Hydrin Cream. The cream hypersensitivity statement reads “The use of Lac-Hydrin Lotion should be discontinued if any hypersensitivity to any of the ingredients is noted. Sun exposure to areas of the skin treated with Lac-Hydrin Lotion should be minimized or avoided (see PRECAUTIONS section).”

Reviewer's recommendation:

Update the WARNINGS section to read as follows: “Sun exposure to areas of the skin treated with Lac-Hydrin Lotion should be minimized or avoided (see PRECAUTIONS section).”

- 4.

A supplement request letter will be drafted to include the recommendations for labeling revisions as listed in items one through four above.

Conclusions

Recommendation: Acknowledge and retain action for NDA 19-155/S-015
 Approvable action for NDA 19-155/S-019
 Approvable action for NDA 19-155/S-020
 Supplement request letter to NDA 19-155.

 Leslie A. Vaccari, BSN, RAC
 Regulatory Project Manager, ODE V

Supervisory Comment/Concurrence:

 Mary Jean Kozma-Fornaro
 Chief, Project Management Staff
 Division of Dermatologic and Dental Drug Products

Drafted: LVaccari/4-29-2003

Revised/Initialed: MJ Kozma-Fornaro/5-27-03

Finalized: LAV/5-28-03

Filename: CSO Review

PM LABELING REVIEW

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

/s/

Leslie Vaccari
5/28/03 01:34:32 PM
CSO

CSO Review

Mary Jean Kozma Fornaro
5/28/03 02:32:39 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-155

Westwood-Squibb Pharmaceuticals, Inc.
Attention: David L. Silberstein
Associate Director, Regulatory Science
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Silberstein:

Please refer to your new drug application (NDA) for Lac-Hydrin[®] (ammonium lactate lotion) Lotion, 12%.

We have recently reviewed the package insert submitted January 24, 2001.

We request that the following changes in the labeling be made to provide adequate information for the safe and effective use of the product.

1. _____
2. _____
3. Update the WARNINGS section to read as follows: "Sun exposure to areas of the skin treated with Lac-Hydrin Lotion should be minimized or avoided (see PRECAUTIONS section). _____"
4. _____

Submit draft labeling as a prior approval supplement to this application. Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes being made.

The supplement should be submitted within 60 days.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.

Director

Division of Dermatologic & Dental Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

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

/s/

John Kelsey
5/28/03 04:35:02 PM
for Dr. Wilkin



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-155/S-019

Bristol-Myers Squibb Pharmaceutical Research Institute
P.O. Box 400
Princeton, NJ 08543-4000

SEP 20 2000

Attention: David Silberstein
Manager, Dossier Planning and Liason Support
Regulatory Dossier Planning and Management

Dear Mr. Silberstein:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Lac-Hydrin 12% (ammonium lactate) Lotion

NDA Number: 19-155

Supplement Number: S-019

Date of Supplement: August 24, 2000

Date of Receipt: August 29, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 28, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Dermatologic and Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Mary J. Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental
Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research

NDA 19-155/S-019

Page 2

cc:

Original NDA 18-738/S-007

HFD-540/Div. Files

HFD-540/CSO/Kevin Darryl White

SUPPLEMENT ACKNOWLEDGEMENT

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

DATE: AUG 2 2000

FROM: Marilyn R. Pitts, Pharm.D.
 Postmarketing Safety Evaluator
 Division of Drug Risk Evaluation I, HFD-430

THROUGH: Julie Beitz, M.D., Director *gouty 8-2-00*
 Division of Drug Risk Evaluation I, HFD-430

TO: Jonathan Wilkin, M.D., Director
 Division of Dermatologic and Dental Drug Products, HFD-540

SUBJECT: Consultation Request - PID# ^{D000532}~~D000525~~ ¹⁹¹⁵⁵
 Drug: Lac-Hydrin 12% Lotion (NDA ~~19555~~) and Cream (NDA 20508)
 Reaction: Adverse Event Review

EXECUTIVE SUMMARY

This document summarizes 190 adverse event reports for Lac Hydrin 12% Lotion (184) and Cream (7). All cases listed Lac-Hydrin cream or lotion as the suspect agent. The patients were predominantly female (119). There were 51 males and 20 patients with an unknown gender. The ages of the patients ranged from eight to 83 years, with a median age of 60. The majority of cases were domestic (187), with the origin of the remaining three cases unknown.

There were several cases with a notable outcome. There was one death reported in a clinical trial patient that was unrelated to the use of Lac-Hydrin. There was one case resulting in hospitalization in a patient with confounding medical history and concomitant product use. The cases reporting disability and treatment with a prescription drug involved one patient who experienced peeling hands, two with a possible allergic reaction, and one who experienced inflammation.

Reactions at the application site constituted the bulk of the adverse events reported. Many of the local reactions are labeled events including burning, stinging, erythema, peeling and hyperpigmentation. Rash was reported frequently (40) and is not clearly a labeled event, although some elements of skin rash are labeled (dryness, eczema, peeling). The reported events of hirsutism, fingernail alterations and skin discoloration such as yellowing or brown spots are not labeled events. It is difficult to determine Lac-Hydrin's role in the aforementioned events due to the paucity of information contained in the reports.

INTRODUCTION

On July 12, 2000 DDDP, HFD-540 submitted a consult requesting a review of postmarketing data of adverse events for Lac-Hydrin (ammonium lactate 12%) cream and lotion for a scheduled efficacy review on August 26, 2000. Lac-Hydrin, (ammonium lactate) is available as a 12% lotion and cream. The lotion is indicated for the treatment of dry, scaly skin (xerosis) and ichthyosis vulgaris and for temporary relief of itching associated with these conditions. Lac-Hydrin Cream is indicated for the treatment of ichthyosis vulgaris and xerosis.

The following precautionary information is expressed in the labeling of both formulations. Adverse events specific to each are listed separately.

Precautions

- For external use only.
- Avoid contact with the eyes, lips or mucous membranes.
- Caution is advised when used on the face of fair-skinned individuals since irritation may occur.
- Stinging or burning may occur when applied to skin with fissures, erosions, or that is otherwise abraded, inflamed, or in individuals with sensitive skin.

Adverse Reactions

Lotion

The most frequent adverse experiences in patients with xerosis are transient stinging (1 in 30 patients), burning (1 in 30 patients), erythema (1 in 50 patients) and peeling (1 in 60 patients). Other adverse reactions, which occur less frequently, are irritation, eczema, petechiae, dryness and hyperpigmentation.

Due to the more severe initial skin conditions associated with ichthyosis; there was a higher incidence of transient stinging, burning and erythema (each occurring in 1 in 10 patients).

Cream

In controlled clinical trials of patients with ichthyosis vulgaris, the most frequent adverse reactions in patients treated with Lac-Hydrin Cream were rash (including erythema and irritation) and burning/stinging. Each was reported in approximately 10-15% of patients. In addition, itching was reported in approximately 5% of patients.

In controlled clinical trials of patients with xerosis, the most frequent adverse reactions in patients treated with Lac-Hydrin Cream were transient burning, in about 3% of patients, stinging, dry skin and rash, each reported in approximately 2% of patients.

LITERATURE

A MEDLINE search of the English-language literature published from 1966-2000 was performed. The MESH terms *Lac-Hydrin* with the major qualifier *adverse effects* was used. This search resulted in no significant citations.

SELECTION AND SUMMARY OF CASES

The AERS database was searched for all adverse event reports for Lac-Hydrin. There were 191 unduplicated cases found, 183 cases of the lotion, and seven cases for the cream, and one of unknown formulation. One case was excluded from review because of illegibility.

Demographics and Case Information

Age: 8 to 83 years old, median 60 (not reported in 162 cases)
Gender: female-119, male-51 (not reported in 20 cases)
Outcome: death-1, hospitalization-1, disability-1, treated with Rx drug-3, not reported or not serious-184
Time to onset: immediate (<1 hour)-12, 1 to 24 hours-2, > 24 hours to 5 years-32 (not reported in 144 cases)
Year: 1985 to 1990-38 cases, 1991 to 1995-95 cases, 1996 to present-58 cases
Location: US-177 (not reported in 13 cases)
Dechallenge: positive-35, negative-8 (not reported in 147 cases)

The following adverse events were reported:

- Local reactions (125) including rash, urticaria, itching, burning, redness, warmth, blisters, acne, dermatitis, edema, inflammation, petechiae, and pain.
- Drug ineffective (30)
- Skin discoloration (8) including yellow streaks on skin, yellow color, brown spots, dark spots, and skin turning black, and skin turning yellow.
- Systemic and local non-skin reactions (7) including allergic rhinitis, runny noses, chronic anxiety, headache, dizziness, acetone breath, coughing, bronchospasms
- Hirsutism (5)
- Fingernail alterations (5) including brittleness, softness, thinning, peeling, ridge formation, splitting and "falling off"
- Gastrointestinal (3) including taste alterations and stomach bloating.
- Genitourinary (2) including vaginitis
- Peripheral swelling of the legs and/or feet (2)
- Ocular (1)
- Cardiopulmonary arrest (1) – clinical trial patient
- Condition aggravated (2)

There was one reported death that did not appear to be related to the use of Lac-Hydrin. The death occurred in a clinical trial patient that died of a cardiovascular event. The patient had a history of congestive heart failure with emphysema and had received Lac-Hydrin twice daily, starting one day prior to his death. However, the patient had also been receiving theophylline, furosemide, oral potassium, digoxin, quinidine, calcium, metaproterenol and prednisone.

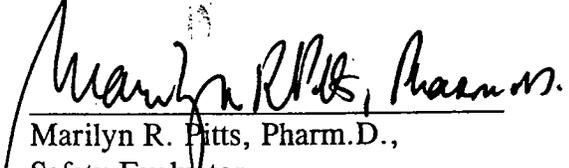
One patient with a significant past medical history required hospitalization. He was an elderly male with a history of diabetic foot ulceration who was hospitalized with red "weepy" areas on his legs after prolonged Lac-Hydrin use. He was also using several other topical products at the time of the event.

The cases reporting disability and treatment with a prescription drug involved one patient who experienced peeling hands, two with a possible allergic reaction, and one who experienced inflammation. The narrative summaries of these cases are included in Appendix 1. One hundred and eighty six cases either reported no outcome, or reported an unknown outcome.

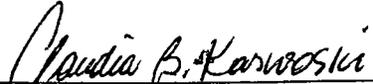
CONCLUSION

One hundred and ninety cases of adverse events were evaluated. All cases listed Lac-Hydrin cream or lotion as the suspect agent. There was one unrelated death case. There were five serious cases attributed to Lac-Hydrin, including one case of hospitalization, one of disability and three cases of treatment by a prescription drug.

Reactions at the application site constituted the bulk of the adverse events reported. Many of the local reactions are labeled events including burning, stinging, erythema, peeling and hyperpigmentation. Rash was reported frequently (40) and is not clearly a labeled event, although some elements of skin rash are labeled (dryness, eczema, peeling). The reported events of hirsutism, fingernail alterations and skin discoloration such as yellowing or brown spots are not labeled events. It is difficult to determine Lac-Hydrin's role in the aforementioned events due to the paucity of information contained in the reports.


Marilyn R. Pitts, Pharm.D.,
Safety Evaluator

Concur:


Claudia B. Karwoski, Pharm.D., Team Leader

Appendix 1. Summary of serious cases and those requiring intervention

Hospitalization

(Direct Report). A 78-year-old male wound clinic patient with a history of diabetic foot ulceration; osteomyelitis and frequent inpatient hospitalizations developed red weepy areas on the legs after prolonged Lac Hydrin lotion use. The patient was also concomitantly using Iodoflex pads, Iodosorb gel, cloderm cream, vancomycin intravenous, ciprofloxacin intravenous and an undetermined cephalosporin antibiotic. The adverse event was reported as abating with discontinuation of Lac Hydrin. No further information is provided.

Disability

(Direct Report). A 35-year-old male experienced itching immediately after washing his hands with chlorhexidine gluconate scrub. After drying his hands, he applied Lac-Hydrin lotion for the itching. The lotion did not stop the itching. The patient experienced some relief when he re-washed his hands. Fourteen days after the use of the chlorhexidine gluconate and Lac-Hydrin the patient experienced peeling of his skin on the palms of his hands and his fingers. The patient reported that the event recurred upon reintroduction of Lac-Hydrin.

Treated with Rx Drug

A 60-year-old female used Lac-Hydrin twice daily for one day. Upon opening the top of the container the patient felt wheezy. She continued to apply the medication that resulted in progressively worse bronchospasms. The patient was concomitantly receiving theophylline, bronchometer and ibuprofen. The report did not provide the drug treatment used for this adverse event. The patient had a history of perfume allergy, and reportedly improved when the Lac-Hydrin was discontinued.

A male patient experienced inflammation of the forehead 4 days after applying Lac-Hydrin lotion. The event resolved with the use of cortisone, but reappeared when the cortisone was discontinued. No further information is provided in this report.

A patient experienced contact irritation with Lac-Hydrin lotion, and a subsequent generalized allergic reaction with Westcort cream. The symptoms did not abate with discontinuation of the product. No further information was provided in this report.