CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-508/S005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

AUG 22 2000

Clinical Pharmacology and Biopharmaceutics Review

Ammonium Lactate 12%
NDA 20-508 SE8-005
LAC-HYDRIN 12%
Reviwer: E.D. Bashaw, Pharm.D.

Westwood Squibb Pharm.
Buffalo, NY 14213

Submission Date:
Aug. 24, 1999

Review of Pediatric Exclusivity Report

Background

Ammonium lactate is the ammonium salt of lactic acid. It is an alpha-hydroxy acid and is applied topically as humectant (i.e., a moisturizing agent). It was approved for this indication in adults in Aug. 1996. At the time of the original approval, the Clinical Pharmacology/Biopharmaceutics portion of the NDA consisted of in vitro work only. This is because lactic acid is a natural byproduct of muscle metabolism and is present in both blood and tissues.

[redacted] in vitro permeation studies were done instead. The results of these studies, using cadaver skin, indicated that only about 6% of the dose was absorbed after 68 hours.

Pediatric Exclusivity

Beginning in Feb. 1999, the sponsor entered into discussions with the Agency regarding a pediatric written request for this product. Subsequently a final written request was issued on Aug. 24, 1999 (see Attachments 1 and 2). This written request included a new in vivo determination of efficacy in patients between the ages of 2-16yrs of age with icthyosis vulgaris (dry, rough, scaly skin). At this time the issue of the need of in vivo pharmacokinetics was re-examined and it was felt that as 2yr old children have fully developed functional skin that the previous in vitro work would be sufficient and that no additional in vivo or in vitro pk work would be required.

Recommendation

No in vivo or in vitro pharmacokinetic data are submitted in this application and none are required from a Clinical Pharmacology/Biopharmaceutics standpoint. No changes have been made to the current package insert regarding pharamacokinetics and none are indicated.

/S/ 8/22/00

E. Dennis Bashaw, Pharm.D.
Senior Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation-III

Secondary Review, Arzu Selen, Ph.D., Dep. Dir. HFD-880, /S/

8/22/2000

CC: NDA 20-508 (ORIG),
HFD-540/DIV File
HFD-540/CSO/WhiteK
HFD-880(Bashaw)
HFD-880(Lazor,Selen)
CDR. ATTN: B. Murphy
HFD-344(Viswanathan)

APPEARS THIS WAY
ON ORIGINAL

Attachment I

6632

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-508

FEB 22 1999

Westwood Squibb pharmaceuticals Inc
Attention: David L. Silberstein
100 Forest Avenue
Buffalo, New York 14213-1091

Dear Mr. Silberstein:

Reference is made to your Proposed Pediatric Study Request submitted on October 20, 1998, for Lac-Hydrin (ammonium lactate cream) Cream, 12%, to NDA 20-508.

To obtain needed pediatric information on Lac-Hydrin (ammonium lactate cream) Cream, 12%, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following study(ies):

Type of study(ies) to be performed:

Randomized, double blind study(ies) to address the safety in roughly equal numbers of children with ichthyosis vulgaris and children with xerosis.

Objective/rationale:

Objective: The objective of this(these) study(ies) is(are) to determine local tolerance and clinical safety of Lac-Hydrin (ammonium lactate cream) Cream, 12%, in children.

Rationale: The rationale for the study(ies) is(are) to obtain clinical safety data to support labeling for pediatric use under the pediatric labeling guidelines established by the FDA.

Indications to be studied: Ichthyosis vulgaris and xerosis.

Study(ies) design:

Multicenter, parallel group, randomized, double blind study(ies), consisting of a 2-week washout, 4-week b.i.d. treatment, and a 2-week follow-up for recurrence.

Age groups in which the study(ies) will be performed:

Children aged 2-16 years, with a minimum of 25% of the enrolled children in the 2 to 6 years of age range and 50% in the 2 to 12 years of age range. Study(ies) could even be limited to 2 year olds, from whom the Agency would extrapolate an acceptable safety profile from 2 year olds up to adulthood.

Number of patients to be studied or the power of the study(ies) to be achieved:

136 patients total (68 active, 68 vehicle)

Entry criteria (i.e., inclusion/exclusion criteria):

Inclusion criteria:

- Children aged 2-16 years with at least moderately severe ichthyosis vulgaris and xerosis.

Exclusion criteria:

- Hypersensitivity to any of the ingredients in the formulation.
- Participant in another investigational study, concurrently or within previous four weeks.
- Use of another topical therapy (including urea, AHAs, etc.) or topical corticosteroids, except bland emollients, within two weeks prior to study entry.
- Use of systemic corticosteroids within four weeks prior to enrollment or during the study.

Clinical endpoints:

Primary safety endpoints: Redness, itching, burning, stinging, scaling, oozing, crusting, vesiculation, worsening of the underlying condition, and urtication.

Study(ies) evaluations: Weekly

Drug information:

Dosage form:	Cream
Regimens:	Twice daily
Route of administration:	Topical
Formulation:	ammonium lactate, 12%

Safety concerns: Excessive local drug irritation

Statistical information:

Descriptive statistics of safety endpoints.

The difference in the weight of tubes returned, compared to the amount dispensed to the subject, will provide an estimate of drug exposure during the study(ies).

Labeling that may result from the study(ies):

Pediatric Use: The safety and effectiveness of Lac-Hydrin Cream, 12%, have been established in children as young as two years of age. Note: The Agency would infer efficacy in the presence of an acceptable safety profile.

Format of report to be submitted to the agency:

Full and final study report addressing issues outlined in this request.

Timeframe:

Full and final study report must be submitted to the Agency by August 28, 1999.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission. We recommend you seek a written agreement, as described in the guidance to industry (Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act), with FDA before developing pediatric protocols. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Kevin Darryl White, Project Manager, at 301 827-2020.

Sincerely yours,

/S/

Robert J. DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Attachment II

6639

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 20-508

Food and Drug Administration
Rockville MD 20857

Westwood-Squibb Pharmaceuticals, Inc.
Attention: David L. Silberstein
100 Forest Avenue
Buffalo, New York 14213-1091

AUG 24 1999

Reference is made to your correspondence dated June 15, 1999, requesting changes to FDA's February 22, 1999, Written Request for pediatric studies for Lac-Hydrin (ammonium lactate cream) Cream, 12%.

We have reviewed your proposed changes and are amending the below listed sections of the Written Request. All other terms stated in our Written Request issued on February 22, 1999, remain the same.

Type of study (ies) to be performed:

Randomized, double blind study(ies) to address the safety in children with ichthyosis vulgaris.

Indications to be studied: Ichthyosis vulgaris.

Number of patient to be studied or the power of the study (ies) to be achieved:

90 patients total (45 active, 45 vehicle)

Entry Criteria (i.e., inclusion/exclusion criteria):

Inclusion Criteria:
- Children aged 2-16 years with at least moderately severe ichthyosis vulgaris.

Exclusion Criteria:
- Use of another topical therapy or topical corticosteroids, except "normally used cosmetics" within two weeks prior to study entry.

Reports of the studies that meet the terms of the Written Request dated February 22, 1999, as amended by this letter must be submitted to the Agency on or before August 28, 1999, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission. To avoid uncertainty, we recommend you seek a written agreement with FDA before developing pediatric studies. Please notify us as soon as

possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

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We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Mary Jean Kozma-Fornaro, Supervisor, Project Management Staff, at 301 827-2020.

Sincerely yours,

/S/

Robert J. DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL