CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-508/S005

CORRESPONDENCE

6628

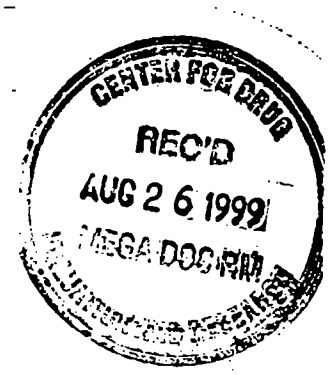
DUPLICATE

SE8-005

WESTWOOD SQUIBB
100 Forest Avenue Buffalo. NY 14213-1091
(716) 887-3400 Fax (716) 887-3751

August 24, 1999

Jonathan Wilkin, M.D. Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9210 Corporate Dr.
Rockville, MD 20850



NDA NO. 20-508 REF. NO. 005

NDA IN FILE FOR SE8

RE: NDA 20-508 LAC-HYDRIN 12%
(ammonium lactate cream) Cream
Supplement #05: Proposed Revised Labeling

Dear Dr. Wilkin:

SUBMISSION OF PEDIATRIC STUDY REPORT PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

Dear Dr. Wilkin:

Reference is made to NDA 20,508, approved August 29, 1996, and to the Written Request for Pediatric Study(ies) dated Feb 22, 1999, as modified by the Agency's response to changes requested in our submission dated March 3, 1999, and subsequent discussions. A revised Written Request was provided to the sponsor on August 24, 1999. Copies of correspondence from FDA are enclosed.

This submission provides proposed labeling changes to reflect pediatric use of this drug product. These changes are detailed in a side-by-side comparison of current and proposed labeling. In support of these changes, this supplement includes a full and final study report addressing the points outlined in the written request as subsequently modified.

A table of contents outlines the information provided in this supplement. A copy of this cover letter is being provided to the Office of Generic Drugs. If you require additional information relating to this submission please contact the undersigned at (716) 887-7680, or via fax at (716) 887-3638. I can also be reached via electronic mail at schrodek@bms.com.

Sincerely,

Kathy B. Schrode

Kathy B. Schrode, Ph. D.
Director, Worldwide Regulatory Affairs

Submitted in duplicate.

Desk copies to Kevin Darryl White [(301) 827-2075] and Mary Jean Kozma-Fornaro [(301) 827-2091]

Copy of Cover letter and table of contents provided via facsimile [(301) 594-0183] to Director, Office of Generic Drugs (HFD-600)Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6483 Fax 609 252-6000

Kathy B. Schrode, Ph.D.
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science

NDA SUPPL AMENDMENT

AMENDMENT TO PENDING SUPPLEMENT S#-005
RESPONSE TO REQUEST FOR INFORMATION

SE8-005 BM

April 27, 2000

NDA 20-508
Lac-Hydrin (ammonium lactate cream) 12% Cream

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
HFD-540
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Wilkin,

Reference is made to our supplemental new drug application (NDA 20-508, S# -005), received at the Agency on August 26, 1999, which responded to a Written Request for a Pediatric Study for Lac-Hydrin (ammonium lactate cream) 12% Cream.

Reference is also made to a telephone contact between Ms. Indira Kumar of the Division and Mr. David Silberstein of Bristol-Myers Squibb on February 16, 2000, in which Ms. Kumar made several requests for information. These requests are briefly outlined below, followed by our response

1. The supplement requires a financial disclosure form. (Form 3454).

   The requested documents are attached. Note that at the time the investigators were queried regarding this requirement.

DUPLICATE

[ ]

2. The medical reviewer requests a listing of all topical products used by subjects during the study other than the study drug.

   Please refer to Listing 9 in the final study report for Study DE109-035 (beginning on page 6856 of the submission), which notes all prior and concomitant medications reported to be used by subjects. Except for Lac-Hydrin, the topical products noted are marketed over the counter as cosmetics. No further information is available on the proprietary mixture listed as "Kirkland moisturizer".

   Note that the requirement for at least moderate severity of the condition at entry ensures that any residual effect of prior topical treatment on safety or efficacy is minimized.

3. For several subjects (#s 38, 39, 41 and 43) identify the exact ammonium lactate product used during the washout period.

   Lac-Hydrin, when listed, may be the lotion or cream dosage form, which are qualitatively identical and contain the same strength of ammonium lactate. It is not immediately possible to determine whether the dosage form of Lac-Hydrin used by these patients was the Lotion or Cream. However, we note that for 3 of the 4 patients reporting Lac-Hydrin use within the indicated period, the start date for such use was before the Cream was first marketed. These patients, prior to the fall of 1996, could only have used the Lotion dosage form, which has always contained labeling permitting pediatric use.

4. Identify the exact body sites treated with ammonium lactate in the subjects noted above and any others who used ammonium lactate products during washout.

   No subjects other than the four noted above used Lac-Hydrin within the two-week period prior to study start. A formal two-week washout was deleted from the protocol in an administrative letter dated March 10, 1999. The administrative letter noted subjects were to refrain from use of topical moisturizers or emollients for 48 hours prior to study start. The subjects noted in comment 3 were enrolled into the study after the administrative letter was issued. All had discontinued Lac-Hydrin use 3 to 4 days prior to the date the informed consent to enter the study was signed, and 3 to 11 days before initiating treatment with study medication.

   There is no information available in Case Report forms on specific body areas treated. Physicians may have noted such information in source documents, but these were not routinely available to the monitor, except to check validity of CRF entries during monitoring visits.

5. The following subjects appeared to have less than 18% BSA treated. Provide CRFs for these subjects and note which areas were treated (if this is noted in the CRF, point out location of information). [Subjects 49, 50, 74, 75, 97, 101, 102, 104, 105, 106, 107, 108, 121, 122, 123, 125, 126, 127.]

   CRFs are provided for the identified subjects. However, these CRFs did not record specific body location information.

If additional information is required to further review of the supplement, please contact me at (609) 252-6463. I can also be reached via facsimile at (609) 252-6000.

Sincerely,

David L Hilbert for KBS

Kathy Schrode, Ph.D.
Group Director, Liaison, Lifestyle Products
Regulatory Science

KS/DS/kb
Cover letters *via* FAX to Indira Kumar and Kevin Darryl White (301) 827-2075

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 4000 Princeton, NJ 08543-4000 609 921-4000

AMENDMENT # 2 TO PENDING SUPPLEMENT S#-005
RESPONSE TO REQUEST FOR INFORMATION

NDA 20-508
Lac-Hydrin (ammonium lactate cream) 12% Cream

May 3, 2000

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
HFD-540
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

NDA SUPPL AMENDMENT

Bm
SE8-005

Dear Dr. Wilkin,

Reference is made to Supplement # S-005 to NDA 20-508, received at the Agency on August 26, 1999. The supplement responded to a Written Request for a Pediatric Study for Lac-Hydrin (ammonium lactate cream) 12% Cream.

Reference is also made to a telephone contact between Ms. Indira Kumar of the Division and Mr. David Silberstein of Bristol-Myers Squibb on February 16, 2000, in which Ms. Kumar made several requests for information, and to a follow-up communication *via* e-mail from Kevin Darryl White on April 18, 2000, requesting additional clarifications. The initial request has been addressed in a recent submission. The subsequent requests are reproduced below, followed by our response.

1. Please clarify the fact that table B in the first volume (21.1) suggests that the total number of patients dispensed medication was 103, yet line listings have the patients up to #143. Even if patients did not come back for the post treatment follow-up, they should be listed for all randomized subjects.

The medication was provided to each investigational site as numbered sets, each tube in the set already labeled with a unique subject number and randomized. The number of medication sets go up to 143, and exceeds the number of patients originally planned to be enrolled at a site, to allow for sites that might be able to enroll additional patients beyond the original projection. Gaps in the numerical sequence, or out of sequence assignments, are not the result of subjects not reported, but merely due to medication sets that were never allocated and dispensed to patients. Even if a patient never returns for follow up, all patients assigned to a treatment are listed in the All Randomized Subjects listing. The total number of subjects enrolled is 103. Subject numbers (001-143) are based on the allocation schedule, not on the actual enrollment, and thus are occasionally out of sequence.

2. Provide a list of patients (from the 143) that were not included in the all randomized subjects.

As there were no patients excluded from the "all randomized subjects" listing, the skipped numbers do not represent patients not reported, but unassigned medication sets, as noted above.

3. Table L does not state the total "N". Please provide.

The Total N for each group is the same as that provided in Table J, 52 for the active and 51 for the vehicle

4. Either tell us the exact location (volume no.) for each of the following CRFs for patients 108, 121, 122, 123, 125, 126 and 127, or send us reviewer copies.

These CRFs have been provided in response to the February 16 request. Please see the recently submitted amendment to Supplement #05.

5. Were SAS data sets submitted with this supplement? If not, are they available?

SAS data sets were not part of the original submission. The data are provided, however, in the desk copy of this submission. Because of the original size of the transport files, they have been provided in zipped format in order to be accommodated on a 3.5" magnetic disk. If you do not have the "unzip" utility, an evaluation version can be downloaded at no charge from the following web site: "http://www.winzip.com." If you have difficulty retrieving the files in this format, please contact me and I will provide the information in an alternative format.

If additional information is required to further review of the supplement, please contact me at (609) 252-4317. I can also be reached via facsimile at (609) 252-6000 or (609) 252-7396.

Sincerely,

David Silberstein
Manager, Dossier Planning and Management
Bristol-Myers Squibb

Desk copy to KD White with magnetic disk containing data sets

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 4000 Princeton, NJ 08543-4000 609 252-4000

AMENDMENT # 3 TO PENDING SUPPLEMENT S#-005
RESPONSE TO REQUEST FOR INFORMATION

NEW CORRESP
NC
405-005

May 23, 2000

NDA 20-508
Lac-Hydrin (ammonium lactate cream) 12% Cream

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
HFD-540
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Wilkin,

Reference is made to Supplement # S-005 to NDA 20-508, received at the Agency on August 26, 1999. The supplement responded to a Written Request for a Pediatric Study for Lac-Hydrin (ammonium lactate cream) 12% Cream.

Reference is also made to a telephone contact between Mr. Kevin Darryl White and Dr. Steven Thomson of the Division and Mr. David Silberstein of Bristol-Myers Squibb on May 19, 2000, in which Dr. Thomson requested a "code book" for Study DE109-035. In response to that request, this submission contains a printout of the "CONTENTS PROCEDURE" reflecting the SAS data set for the study, which provides detailed information regarding each variable.

If additional information is required to further review of the supplement, please contact me at (609) 252-4317. I can also be reached via facsimile at (609) 252-6000 or (609) 252-7396.

Sincerely,

David Silberstein
Manager, Dossier Planning
and Management
Bristol-Myers Squibb

Desk copy to KD White (full copy)

APPEARS THIS WAY
ON ORIGINAL