CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-307

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-307

DEC -7 2001

Schering-Plough HealthCare Products
Attention: Mary E. Williams,
Associate Director, Regulatory Affairs
Three Connell Drive
P.O. Box 603
Berkeley Heights, New Jersey 07922-0603

Dear Ms. Williams:

Please refer to your new drug application (NDA) dated September 28, 2000, received September 29, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for butenafine hydrochloride cream, 1%.

Please also refer to our Approvable Letter for Lotrimin Ultra butenafine hydrochloride cream 1% dated July 27, 2001.

We acknowledge receipt of your submissions dated October 5, November 5, and December 3 and 7 (facsimile), 2001.

This new drug application provides for the use without prescription of Lotrimin Ultra butenafine hydrochloride cream 1%, for the topical treatment of the following superficial dermatophytoses: interdigital tinea pedis (athlete's foot), tinea corporis (ringworm) and tinea cruris (jock itch) due to *E. floccosum, T. mentagrophytes, T. rubrum,* and *T. tonsurans.*

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels) and must be formatted in accordance with the requirements of 21 CFR 201.66. Marketing the product with FPL that is not identical to the approved labeling text and "Drug Facts" format may render the product misbranded and an unapproved new drug.

We note that copies of final printed labeling (FPL) have been submitted on October 5, 2001.

We remind you of your postmarketing study commitments in your submissions dated July 25, December 3 and 7 (facsimile), 2001. These commitments are listed below.

1. Conduct a study to test consumers' ability to differentiate the Lotrimin AF labeling from the Lotrimin Ultra labeling in terms of distinguishing the different active ingredients

Protocol Submission:	Within 1 month of the date of this letter submit the protocol for Agency review and approval.
Study Start:	Within 3 months of the date of this letter initiate the study.
Final Report Submission:	Within 6 months of the date of this letter submit the final report.

2. Conduct a study to evaluate the safety of this drug for tinea corporis in the 2 - 12 year old pediatric population. This study should include pharmacokinetic sampling (systemic absorption data under maximal use conditions) and a comprehensive evaluation of local intolerance. Any additional information regarding local effects in children may be submitted, if available.

Protocol Submission:	Within 3 months of the date of this letter submit the protocol for Agency review and approval and any additional information regarding local effects in children.
Study Start:	Within 6 months of the date of this letter initiate the study.
Final Report Submission:	Within 16 months of the date of this letter submit the final report.

3. Conduct a study to evaluate the efficacy of this drug for tinea corporis in the 2 - 12 year old pediatric population, especially since the dermatophyte species responsible may vary from adults. Alternatively, information may be submitted that demonstrates that the dermatophyte species responsible for tinea corporis in the 2 - 12 year old pediatric population does not vary from adults. If this information is demonstrated, the need for an efficacy study could be waived.

Protocol Submission:	Within 3 months of the date of this letter submit the protocol and alternative information for Agency review and approval.
Study Start:	Within 9 months of the date of this letter initiate the study, if the FDA concludes that the alternative information is not convincing.
Final Report Submission:	Within 19 months of the date of this letter submit the final report.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study.

All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). Because of the low prevalence of tinea cruris and tinea pedis in the 12 year old and under pediatric population these indications would be difficult to study and are waived. Additionally, because of the low prevalence of tinea corporis in the 2 year old and under pediatric population this indication would be difficult to study and is waived. We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27) for pediatric studies in pediatric patients aged 2 – 12 years old for tinea corporis. We are deferring submission of these pediatric studies until April 7, 2003, for the pediatric safety study and July 7, 2003, for the pediatric efficacy study. We note your submission of a protocol to study tinea corporis in the 2 – 12 year old pediatric population.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit two copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Dermatologic & Dental Drug Products, one to the Division of Over-the-Counter Drug Products. For administrative purposes, this submission should be sent to the NDA and should be identified as a correspondence to approved NDA 21-307.
Please submit one market package of the drug product when it is available.

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

In line with Center for Drug Evaluation and Research policy, oversight of this application is being transferred to the Division of Over-the-Counter Drug Products. If you have any questions, please contact Daniel Keravich, Regulatory Health Project Manager, at (301) 827-2222.

Sincerely,

/S/
{See appended electronic signature page}

Charles Ganley, M.D.
Director
Division of Over-The-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

/S/
{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

Enclosure

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JUL 27 2001

Schering-Plough HealthCare Products
Attention: Mary E. Williams,
Associate Director, Regulatory Affairs
Three Oak Way
P.O. Box 603
Berkeley Heights, New Jersey 07922-0603

Dear Ms. Williams:

Please refer to your new drug application (NDA) dated September 28, 2000, received September 29, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotrimin Ultra butenafine HCl cream, 1%.

We acknowledge receipt of your submissions dated September 29, October 12, 13, 19 and 25, November 22, and December 7, 2000; January 31, February 21, March 8 and 14, May 3 and 22, June 8 and July 12, 18, 19, 23 and 25 (2), 2001.

This new drug application provides for the use without prescription of Lotrimin Ultra butenafine hydrochloride cream, 1%, for the topical treatment of interdigital tinea pedis (athlete's foot between the toes), tinea corporis (ringworm) and tinea cruris (jock itch).

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the investigator. Satisfactory inspections will be required before this application may be approved.

Also, you should propose a protocol to satisfy a Post Marketing Commitment to evaluate the safety and efficacy of tinea corporis in the 12 year old and under pediatric population, especially since the dermatophyte species responsible may vary from adults.

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the immediate container and outer carton labels).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.
Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632).

We remind you of your postmarketing study commitment in your submission dated July 25, 2001. This commitment is listed below.

Conduct a study to test consumers' ability to differentiate the Lotrimin AF labeling from the Lotrimin Ultra labeling in terms of distinguishing the different active ingredients

Protocol Submission:	Within 1 month of the date of this letter submit the protocol for Agency review and approval.
Study Start:	Within 3 months of the date of this letter initiate the study.
Final Report Submission:	Within 6 months of the date of this letter submit the final report.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug.

The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, please submit two copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Dermatologic & Dental Drug Products, one to the Division of Over-the-Counter Drug Products. For administrative purposes, this submission should be sent to the NDA and should be identified as a correspondence to NDA 21-307.

Within 10 days after the date of this letter, you are required to amend the 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 any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies 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.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

/S/

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Division of Over-The-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

/S/

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
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Enclosure

24 pages redacted from this section of the approval package consisted of draft labeling