

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-010

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW
CONSULTATION FOR DIVISION OF DERM & DENTAL DRUG PRODUCTS

NDA#: 20-010 **REVIEW #:** 1 **COMPLETED DATE:** 10/02/00

| <u>DOCUMENT TYPE</u> | <u>DOCUMENT DATE</u> | <u>REC'D by HFD-520</u> | <u>ASSIGNED DATE</u> |
|----------------------|----------------------|-------------------------|----------------------|
| BI NE | 06/08/00 | 06/15/00 | 06/15/00 |
| FAX | 09/27/00 | 09/29/00 | 09/29/00 |

NAME & ADDRESS OF APPLICANT:

Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

CONTACT PERSON(s):

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs
Tel: (908) 740-2628

or

Ellen R. Thelan
U.S. Regulatory Affairs
Tel: (908) 740-2628

SUBMISSION & FAX REVIEWED:
PROVIDES FOR:

The Applicant's response, 06/08/00, to the microbiology questions made via telephone conversations on 02/23/00 and 03/01/00, respectively. This includes draft labeling on the **CLINICAL PHARMACOLOGY – Microbiology** subsections. Also, the Applicant's FAX, 09/27/00, containing revised draft labeling for LOTRISONE Cream and Lotion.

DRUG PRODUCT NAME:

Clotrimazole

| | |
|-------------------------|-------------------|
| <u>Proprietary:</u> | Clotrimazole |
| <u>Non-Proprietary:</u> | clotrimazole |
| <u>Chemical Type:</u> | Azole (imidazole) |
| <u>CAS No:</u> | CAS-23593-75-1 |

Betamethasone Dipropionate:

| | |
|-------------------------|---------------------------------|
| <u>Proprietary:</u> | Betamethasone Dipropionate |
| <u>Non-Proprietary:</u> | betamethasone dipropionate |
| <u>USAN:</u> | betamethasone dipropionate |
| <u>Chemical Type:</u> | Glucocorticoid (corticosteroid) |
| <u>CAS No:</u> | CAS-5593-20-4 |

Clotrimazole / Betamethasone dipropionate:

Code: SCH 370, Bay b 5097

SCHERING CORPORATION Inc.

(clotrimazole and betamethasone dipropionate) LOTION®

CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA, MOL. W.T.:**Clotrimazole:**

Chemical Name/Structure = See 2000 USAN (pp. 183)
Molecular Formula = C₂₂H₁₇ClN₂
Molecular Weight = 344.84

Betamethasone dipropionate:

Chemical Name/Structure = See 2000 USAN (pp. 91)
Molecular Formula = C₂₈H₃₇FO₇
Molecular Weight = 504.59

DOSAGE FORM: Lotion

STRENGTH: 1% clotrimazole / 0.05% betamethasone

Clotrimazole: Each gram of lotion contains 10 mg clotrimazole;

Betamethasone dipropionate: Each gram of lotion contains 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone).

ROUTE OF ADMINISTRATION: Topical

DISPENSED: Rx

PHARMACOLOGICAL CATEGORY / INDICATION(s):

Clotrimazole is a synthetic antifungal (imidazole) agent. Betamethasone dipropionate is a synthetic corticosteroid. /

The combination product is indicated for _____

Note: For non-inflamed tinea, tinea cruris, and tinea corporis, effective treatment may be obtained using a topical antifungal agent that does not contain a corticosteroid.

RELATED DOCUMENTS:

NDA 18-827, Lotrisone® (clotrimazole / betamethasone dipropionate) Cream, Approved 07/10/84.

CONSULTS: This submission and FAX are "consults" from the Division of Dermatological and Dental Drug Products (DDDDP/HFD-540).

SCHERING CORPORATION Inc.

(clotrimazole and betamethasone dipropionate) LOTION®

REMARKS/COMMENTS:

The original application was dated August 31, 1989. This NDA was made "approvable" on July 31, 1991.

This Microbiology review is on the most recent submission, dated 06/08/00, and FAX, dated 09/27/00. The Applicant responded to a list of questions from the Agency. Proposed draft labeling is provided in the submission and revised labeling is provided in the FAX.

CONCLUSIONS:

The Applicant provided responses, although not all complete, to the Agency's questions. However, there should be an action taken on the labeling on the most current data available.

Therefore, from the microbiological perspective, an approval letter should be issued to the Applicant after negotiations of the revised draft labeling on the CLINICAL PHARMACOLOGY -- Microbiology subsections, respectively, as found on page 10.

THE AGENCY'S MICROBIOLOGY QUESTIONS AND THE APPLICANT'S RESPONSES

On 02/23/2000 and 03/01/2000 there were telephone conversations between the Applicant and DDDDP (HFD-540). The Applicant was requested to respond to the following microbiology questions:

Agency's Request #1 (February 23, 2000):

Provide study reports from the original NDA for antibiotic activity against *Microsporium canis*. The July'91 label contains *in vitro* activity. The reports of studies demonstrating this activity should be provided.

Applicant's Response #1:

Schering stated that no study reports were submitted in the Lotrisone Lotion NDA. The references in NDA 20-010 were made to the Lotrisone Cream and Lotrimin NDA. Activity against *Microsporium* spp. and *Microsporium canis* isolates are provided in the reference papers (Nos. 2,4,5,7,8, & 9) in this submission.

Microbiologist's Comment #1:

The Applicant did provide data on the activity of clotrimazole against *Microsporium* species and *Microsporium canis*. The activity data are referenced from the Lotrisone Cream and Lotrimin NDAs. These studies are not current and are outdated (i.e., 5 = 1971 to 1974 and 1 = 1980).

Agency's Request #2 (February 23, 2000):

Complete reports should include design and results. In the results, how many isolates were tested and what were the sources of isolates.

SCHERING CORPORATION Inc.

(clotrimazole and betamethasone dipropionate) LOTION®

Microbiologist's Comment #2:

The Applicant did provide information in reports as peer-reviewed journals. The total number of isolates tested and the sources of the isolates, except for one source – Reference #7) are given. Both *Microsporium* spp. and *Microsporium canis* isolates are provided.

The total number of isolates for *Microsporium canis* is small (≤ 70). More significantly, the subject application is for a lotion and susceptibility testing results for interpretative criteria breakpoints (MICs) are correlated to systemic (blood drug concentrations) related indications and infections and not to topical use. The activity data were referenced from the Lotrisone Cream and Lotrimin NDAs. These studies are not current and are outdated (i.e., 5 = 1971 to 1974 and 1 = 1980).

Agency's Request #3 (February 23, 2000):

Were the studies conducted using clotrimazole alone, betamethasone dipropionate, alone or a combination.

Microbiologist's Comment #3:

The Applicant stated that all the *in vitro* studies used clotrimazole. However, the Applicant did provide an *in vitro* animal model study by Loebenberg, D-Report 13629, Reference #6, and dated 1983. In the study, the combination product and the individual components were tested by *in vitro* methods. However, no new information on the lotion formulation was submitted. The investigator used creams and ointments in this study and the subject NDA is a lotion. provided. Also, the formulations of the drug products have different vehicle compositions.

Agency's Request #4 (February 23, 2000):

A literature search on *Microsporium canis* should be provided and annotate the labeling.

Agency's Comment #4 (March 1, 2000):

Dr. Bala, FDA, was also looking for additional microbiology information, literature searches, that might be available since 1991. Schering should provide annotation for the review of the labeling changes pertaining to microbiology.

Microbiologist's Comment #4:

The Applicant did perform literature searches and did provide abstracts on clotrimazole and clotrimazole / betamethasone dipropionate.

The provided information is incomplete. Full study articles are not provided, only abstracts. The available abstracts contained *in vitro* and animal data on dermatophytes. In many abstracts, available data on *Microsporium canis* are not explicitly stated. In some cases, an indication or infection are stated, but not the organisms. Some abstracts contained information on fungal infections and indications not approved in this NDA.

Note: In one abstract, Schering Drug: 000370, LOTRISONE – Clotrimazole and Bethamethas91022002A, LOTRISONE (ALAS) REVISITED, Citation: SCHOCH Letter, 12/90 (Letter to the Editor), on page 8, the author thought "that treatment failures and exacerbations with topical Lotrisone were because of immune suppression of the potent topical steroid with a weak antifungal agent.

SCHERING CORPORATION Inc.

(clotrimazole and betamethasone dipropionate) LOTION®

Agency Request #5 (February 23, 2000):

The microbiology that would appear in the PI should be organized in a format consistent with today's guidelines (4 subheadings).

Agency's Request #3 (March 1, 2000):

An updated **MICROBIOLOGY** labeling section with the following 4 subsections should be included as in "AmBisome for Injection", **Mechanism of Action**, **Activity In Vitro**, **Activity In Vivo**, and **Drug Resistance**.

Applicant's Response #5:

The Applicant reorganized and updated the **Clinical Pharmacology** section of the labeling into the **CLINICAL PHARMACOLOGY** section and the **MICROBIOLOGY** subsection. Also, information for the **Activity In Vivo** has been added with references.

LOTRISONE® Cream and Lotion Package Insert Labeling (NDA 20-010)**MICROBIOLOGY**

The Applicant provided, dated 05/04/2000, proposed draft labeling – **MICROBIOLOGY**, on page 28, and annotated "draft" *Microbiology* labeling, dated 05/04/00, on page 30, for Lotrisone Lotion.

After discussions with, Dr. Albert Sheldon, DDDDP (HFD-540) and the Lotrisone Team Medical Officers the following microbiology labeling for the LOTRISONE Package Insert is recommended:

CLINICAL PHARMACOLOGY**Clotrimazole**

The **CLINICAL PHARMACOLOGY – MICROBIOLOGY** annotated draft labeling, on page 30, is revised and updated as described:

MICROBIOLOGY:**1. Mechanism of Action:**

- a. The first and second described paragraphs are deleted:

(clotrimazole and betamethasone dipropionate) LOTION®

Microbiologist's Comments:

The first sentence of the first paragraph is revised, updated, and moved to the **Activity In Vitro** subsection. The second sentence is deleted.

The second paragraph is deleted, because: (1) The references only cited *Candida albicans* and is not found in the INDICATIONS AND USAGE section) and (2) The information is outdated.

Therefore, the **Mechanism of Action** subsection is revised and updated, as described:

Clotrimazole is an imidazole antifungal agent. Imidazoles inhibit 14- α -demethylation of lanosterol in fungi by binding to one of the cytochrome P-450 enzymes. This leads to the accumulation of 14- α -methylsterols and reduced concentrations of ergosterol, a sterol essential for a normal fungal cytoplasmic membrane. The methylsterols may affect the electron transport system, thereby inhibiting growth of fungi.^{a,b,c}

b. Applicant's FAX, dated 09/27/00:

Under the **Mechanism of Action** subsection, in the 3rd line, revise "14—methylsterols" to read "14- α -methylsterols".

2. Activity In Vivo:

a. The "Activity In Vivo:" subsection is moved and placed as the second subsection heading under **MICROBIOLOGY**.

Activity In Vivo:

b. Delete the described paragraph:

Microbiologist's Comments: The labeling in this subsection, **Activity In Vivo:**, is deleted. Only information on human clinical trials, using the combination drug product, LOTRISONE Lotion, is written in this subsection. Animal supportive data are submitted to the IND/NDA.

The following current labeling is now added and described, as follows:

Activity In Vivo: Clotrimazole has been shown to be active against most strains of the following dermatophytes, both *in vitro* and in clinical infections, as described in the **INDICATIONS AND USAGE** section:

Epidermophyton floccosum, *Trichophyton mentagrophytes*, and *Trichophyton rubrum*.

SCHERING CORPORATION Inc.

(clotrimazole and betamethasone dipropionate) LOTION®

c. Applicant's FAX, dated 09/27/00:

Under the Activity *In Vivo*: subsection, in the 3rd line, revise "Indications and Usage", to read "INDICATIONS AND USAGE". This labeling is capitalized and bolded according to the "TO ALL NDA HOLDERS" letter and dated January 26, 1993.

The Applicant deleted the following described labeling: _____
The Applicant did not provide any reason for deleting this labeling. The labeling statement remains.

3. Activity *In Vitro*:

a. Delete the following described statement:

Microbiologist's Comments:

The statement mentions the terms "fungistatic and fungicidal activity" and is problematic for dermatophytes. At this time the terms are deleted.

In DDDDP, there is a concern on listing fungi in this subsection that are not listed in the INDICATIONS AND USAGE section e.g., *Microsporum canis*. The labeling statement may convey a subtle suggestion that clotrimazole might probably be efficacious against *Microsporum canis*, although there are no supportive clinical studies on the efficacy of clotrimazole against this dermatophyte in this submission.

b. Delete the following described statement:

Microbiologist's Comments: The labeling statement is deleted, because: 1) The data should be restricted to the subject drug, clotrimazole, 2) The labeling statement is promotional -- The other 2-antifungal agents are not in the same class of antifungal drugs, imidazoles, as clotrimazole, and 3) The provided references on "in vitro" data are outdated.

c. The described labeling from MICROBIOLOGY – 1. Mechanism of Action: is deleted:

Add the updated described labeling:

In vitro, clotrimazole has been shown to have activity against most dermatophytes, but the clinical significance is unknown.

(clotrimazole and betamethasone dipropionate) LOTION®

d. Applicant's FAX, dated 09/27/00:

– Under the **Activity *In Vitro***: subsection, in the 2nd and 3rd lines, the Applicant deleted and used the described labeling: , but the clinical significance is unknown. as a separate sentence.

The described labeling: "~~*In vitro*, clotrimazole has been shown to have activity against most dermatophytes, but the clinical significance is unknown.~~" is to remain and to be underlined and bolded according to the "TO ALL NDA HOLDERS letter and dated January 26, 1993.

Note: See next Microbiologist's Comments:

– The Applicant moved the following described labeling from the **Activity *In Vivo***: subsection to the **Activity *In Vitro***: subsection:

"*In vivo* studies in guinea pigs infected with *Trichophyton mentagrophytes* have shown no measurable loss of clotrimazole activity due to combination with betamethasone dipropionate."

Microbiologist's Comments: The complete **Activity *In Vitro***: subsection is now deleted. The Applicant's supportive animal data for this labeling claim is old and outdated.

-- The Applicant moved the following described labeling from the **INDICATIONS AND USAGE** section to this subsection, **Activity *In Vitro***:

"Several cases of treatment failure of LOTRISONE Cream in the treatment of infections caused by *Microsporum canis* have been reported." The labeling statement is to remain in the "INDICATIONS AND USAGE" section. The labeling refers to "treatment failure" which is clinical information and belongs in the "INDICATIONS AND USAGE" section.

4. Drug Resistance:

Drug Resistance: Strains of ~~some~~ dermatophytes having a natural resistance to clotrimazole ~~have~~ have not been reported^{4,7,8}. Resistance to azoles including clotrimazole has been reported in some *Candida* species.

No single-step or multiple-step resistance to clotrimazole has developed during successive passages of *Trichophyton mentagrophytes*⁶.

Microbiologist's Comments: The labeling claim in the 1st sentence of the 1st paragraph is supported by Reference #7 (p. 82) and Reference "d". Reference #8 (not #6) supports the 2nd paragraph labeling claim. See Reference #8, paragraph on left side of page 90, "We also tested.....or *Trichophyton* and *Aspergillus*."

5. Remaining Labeling: See Amendment to NDA 20-010, Lotrisone Lotion, Vol. 1, 2. Labeling Product Information, on Page 4, submitted 10/07/99:

The described labeling on the 1-% cream and 1%-solution is not to be placed in the **MICROBIOLOGY** subsection.

SCHERING CORPORATION Inc.

(clotrimazole and betamethasone dipropionate) LOTION®

Applicant's References for Labeling Annotation

The Applicant provided the following references to support the claims in the proposed labeling for LOTRISONE Lotion:

REFERENCES:

1. Harvey, SC. "Antifungal Drugs. Imidazoles", in Goodman and Gilman's The Pharmacological Basis of Therapeutics, Edited by Gilman, AG et al, 6th Ed, Macmillan Publishing Co., New York, 1980, pp. 982-983.
2. Holt, RJ. "The Imidazoles", in Antifungal Chemotherapy, Edited by Speller, DCE, Wiley & Sons, New York, 1980, pp. 107-125, 142-147.
3. "Antifungal drugs. Clotrimazole", in AMA Drug Evaluations, AMA Department of Drugs, American Medical Association, Chicago, 1980, pp. 1358-1359.
4. Shadomy, S. "In Vitro antifungal activity of clotrimazole", Infect Immun 4:143-148, 1971.
5. Waitz, JA, et al. "Chemotherapeutic evaluation of clotrimazole", Appl Microbiol 22:891-898, 1971.
6. "Clotrimazole-Diprosone *In vivo*" D-Report 13629; Lotrisone Cream NDA 18-827, submitted December 23, 1983, Volume 1.3, Pharmacology References 1.
7. Plempel, M et al. "A new group of orally effective antimycotic substances", Proceedings of the Sixth International Congress of Chemotherapy, Tokyo, 1969, Vol 1, 1970, pp. 138-141.
8. Plempel, M and Bartmann, K. "Experimentelle Untersuchungen zur Antimykotischen Wirkung von Clotrimazol *in vitro* und bei lokaler Applikation *in vitro*", Arzneim Forsch 22:1280-1289, 1972. English version - Drugs Made in Germany 15:103-120, 1972.
9. Holt, RJ. "Recent Developments in Antimycotic Chemotherapy", Infection 2:95-107, 1974.

Review Microbiologist's References**

- a. Hardman, J.G., L.E. Limbird, et al. 1996. GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS. McGraw-Hill Companies, Inc. Ninth Edition:1180-1181.
- b. Mandell, G.L., J.E. Bennett, and R. Dolin. 1995. Mandell, Douglas and Bennett's Principles and Practice of INFECTIOUS DISEASES. Churchill Livingstone. Fourth Edition:407.
- c. Murray, P.R., E.J. Baron, M.A. Pfaller, F.C. Tenover, and R.H. Tenover. 1999. Manual of CLINICAL MICROBIOLOGY. ASM. Seventh Edition:1643.
- d. Hardman, J.G., L.E. Limbird, et al. 1996. GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS. McGraw-Hill Companies, Inc. Ninth Edition:1181,1185.
- e. Samson C., E. Peets, R. Winter-Sperry, and H. Wolkoff. 1992. Clotrimazole/Betamethasone Dipropionate - Lotrisone® - An Antifungal/Steroid Combination for treatment of Cutaneous Dermatophyte Infections. Topical Corticosteroids. 320.

SCHERING CORPORATION Inc.

 (clotrimazole and betamethasone dipropionate) LOTION®

HFD-540/MO/MLuke

HFD-880/BioPharm/SLee

HFD-540/PharmTox/PBrown

HFD-540/Chem/STurujman

HFD-540/ProjMgr/FCross, Jr.

HFD-520/Rev by HVS:09/14;09/28/00

Filename: 20010.FIN

APPROVAL

**APPEARS THIS WAY
ON ORIGINAL**