CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-713/S-017

Trade Name: Mycelex Troche 10 mg

Generic Name: clotrimazole

Sponsor: Bayer Corporation Pharmaceutical Division

Approval Date: March 26, 2001

Indications: For the local treatment of oropharyngeal candisis.

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APPLICATION NUMBER:

18-713/S-017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-713/S-017

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-713/S-017

Bayer Corporation Pharmaceutical Division
Attention: Robin M. Christoforides
Assistant Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear : Ms. Christoforides:

Please refer to your supplemental new drug application dated January 22, 2001, received January 23, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mycelex (clotrimazole) Troche 10 mg.

This "Changes Being Effected in 30 days" supplemental new drug application provides for the alternate drug substance manufacturing site, [redacted] manufacture of clotrimazole drug substance.

We have completed the review of this supplemental application, and it is approved.

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 Frank H. Cross, Jr., Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader for the
Division of Dermatologic & Dental Drug Products,
(HFD-540)
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

/s/

Wilson H. DeCamp
3/26/01 01:53:18 PM
approved

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APPLICATION NUMBER:

18-713/S-017

LABELING

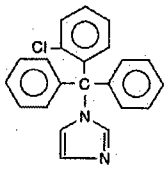
MYCELEX®

(clotrimazole) TROCHE

FOR TOPICAL ORAL ADMINISTRATION

DESCRIPTION Each Mycelex® Troche contains 10 mg clotrimazole [1-(o-chloro-α,α-diphenylbenzyl) imidazole], a synthetic antifungal agent, for topical use in the mouth.

Structural Formula:



Chemical Formula:

$C_{22}H_{17}ClN_2$

The troche dosage form is a large, slowly dissolving tablet (lozenge) containing 10 mg of clotrimazole dispersed in dextrose, microcrystalline cellulose, povidone, and magnesium stearate.

CLINICAL PHARMACOLOGY Clotrimazole is a broad-spectrum antifungal agent that inhibits the growth of pathogenic yeasts by altering the permeability of cell membranes. The action of clotrimazole is fungistatic at concentrations of drug up to 20 mcg/mL and may be fungicidal *in vitro* against *Candida albicans* and other species of the genus *Candida* at higher concentrations. No single-step or multiple-step resistance to clotrimazole has developed during successive passages of *Candida albicans* in the laboratory; however, individual organism tolerance has been observed during successive passages in the laboratory. Such *in vitro* tolerance has resolved once the organism has been removed from the antifungal environment.

After oral administration of a 10 mg clotrimazole troche to healthy volunteers, concentrations sufficient to inhibit most species of *Candida* persist in saliva for up to three hours following the approximately 30 minutes needed for a troche to dissolve. The long term persistence of drug in saliva appears to be related to the slow release of clotrimazole from the oral mucosa to which the drug is apparently bound. Repetitive dosing at three hour intervals maintains salivary levels above the minimum inhibitory concentrations of most strains of *Candida;* however, the relationship between *in vitro* susceptibility of pathogenic fungi to clotrimazole and prophylaxis or cure of infections in humans has not been established.

In another study, the mean serum concentrations were 4.98 ± 3.7 and 3.23 ± 1.4 nanograms/mL of clotrimazole at 30 and 60 minutes, respectively, after administration as a troche.

INDICATIONS AND USAGE Mycelex® Troches are indicated for the local treatment of oropharyngeal candidiasis.The diagnosis should be confirmed by a KOH smear and/or culture prior to treatment.

Mycelex® Troches are also indicated prophylactically to reduce the incidence of oropharyngeal candidiasis in patients immunocompromised by conditions that include chemotherapy, radiotherapy, or steroid therapy utilized in the treatment of leukemia, solid tumors, or renal transplantation. There are no data from adequate and well-controlled trials to establish the safety and efficacy of this product for prophylactic use in patients immunocompromised by etiologies other than those listed in the previous sentence. (See DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS Mycelex® Troches are contraindicated in patients who are hypersensitive to any of its components.

WARNING Mycelex® Troches are not indicated for the treatment of systemic mycoses including systemic candidiasis.

PRECAUTIONS Abnormal liver function tests have been reported in patients treated with clotrimazole troches; elevated SGOT levels were reported in about 15% of patients in the clinical trials. In most cases the elevations were minimal and it was often impossible to distinguish effects of clotrimazole from those of other therapy and the underlying disease (malignancy in most cases). Periodic assessment of hepatic function is advisable particularly in patients with pre-existing hepatic impairment.

Since patients must be instructed to allow each troche to dissolve slowly in the mouth in order to achieve maximum effect of the medication, they must be of such an age and physical and/or mental condition to comprehend such instructions.

Carcinogenesis: An 18 month dosing study with clotrimazole in rats has not revealed any carcinogenic effect.

Usage in Pregnancy: Pregnancy Category C: Clotrimazole has been shown to be embryotoxic in rats and mice when given in doses 100 times the adult human dose (in mg/kg), possibly secondary to maternal toxicity. The drug was not teratogenic in mice, rabbits, and rats when given in doses up to 200, 180, and 100 times the human dose.

Clotrimazole given orally to mice from nine weeks before mating through weaning at a dose 120 times the human dose was associated with impairment of mating, decreased number of viable young, and decreased survival to weaning. No effects were observed at 60 times the human dose. When the drug was given to rats during a similar time period at 50 times the human dose, there was a slight decrease in the number of pups per litter and decreased pup viability.

There are no adequate and well controlled studies in pregnant women. Clotrimazole troches should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PEDIATRIC USE Safety and effectiveness of clotrimazole in children below the age of 3 years have not been established; therefore, its use in such patients is not recommended.

The safety and efficacy of the prophylactic use of clotrimazole troches in children have not been established.

GERIATRIC USE Clinical studies of clotrimazole did not include sufficient numbers of subjects aged 65 and over to determine whether they responsd differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS Abnormal liver function tests have been reported in patients treated with clotrimazole troches; elevated SGOT levels were reported in about 15% of patients in the clinical trials (See Precautions section).

Nausea, vomiting, unpleasant mouth sensations and pruritus have also been reported with the use of the troche.

OVERDOSAGE No data available.

DRUG ABUSE AND DEPENDENCE No data available.

DOSAGE AND ADMINISTRATION Mycelex® Troches are administered only as a lozenge that must be slowly dissolved in the mouth. The recommended dose is one troche five times a day for fourteen consecutive days. Only limited data are available on the safety and effectiveness of the clotrimazole troche after prolonged administration; therefore, therapy should be limited to short term use, if possible.

For prophylaxis to reduce the incidence of oropharyngeal candidiasis in patients immunocompromised by conditions that include chemotherapy, radiotherapy, or steroid therapy utilized in the treatment of leukemia, solid tumors, or renal transplantation, the recommended dose is one troche three times daily for the duration of chemotherapy or until steroids are reduced to maintenance levels.

HOW SUPPLIED Mycelex® Troches, white discoid, uncoated tablets are supplied in bottles of 70 and 140. Mycelex® Troches are also available for institutional use in foil packages of 70 tablets. Each tablet will be identified with the following: Mycelex 10.

	Strength	NDC Code	Tablet Identification
Bottles of 70:	10 mg	NDC 17314-9400-1	MYCELEX 10
Bottles of 140:	10 mg	NDC 17314-9400-3	MYCELEX 10
Unit Dose Package of 70:	10 mg	NDC 17314-9400-2	MYCELEX 10

Store below 86°F (30°C).
Avoid freezing.

Rx Only

TM

alza
PHARMACEUTICALS

Manufactured by Bayer Corporation
West Haven, CT 06516

Distributed by ALZA Pharmaceuticals
A Division of ALZA Corporation
Mountain View, CA 94043

PD500187 BAY 5097 10437 4/01 Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-713/S-017

CHEMISTRY REVIEW(S)

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 18-713 **REVIEW #: 1** **REVIEW DATE: 03/22/01**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SCM-017	22-JAN-2001	23-JAN-2001	16-FEB-2001

NAME & ADDRESS OF APPLICANT: Bayer Corporation Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516

DRUG PRODUCT NAME

Proprietary:	Mycelex® Troche
Established:	1-(o-chloro-α, α-diphenylbenzyl) imidazole
Code Name:	[redacted]
Product Number:	n/a
Chem.Type/Ther.Class:	3S

PHARMACOL. CATEGORY/INDICATION:
DOSAGE FORM: Troche
STRENGTHS: 10 mg
ROUTE OF ADMINISTRATION: Oral lozenge
Rx/OTC: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
1-(o-chloro-α, α-diphenylbenzyl) imidazole
CAS Number: 23593-75-1
Molecular Formula: $C_{22}H_{17}ClN_2$
Molecular Weight: [redacted]

SUPPORTING DOCUMENTS (if applicable): [redacted], December 21, 2000; NDA 18-713/SCM-14.

REMARKS/COMMENTS:
This CBE-30 supplemental new drug application provides for the alternate drug substance manufacturing site, [redacted] clotrimazole drug substance.

The proposed alternate site is [redacted] (SCM 014). The drug substance is produced and tested by the approved specifications and methods.

The Office of Compliance recommendation is ACCEPTABLE per EER dated February 27, 2001.

CONCLUSIONS & RECOMMENDATIONS:
Recommend approval action.

Mamta Gautam-Basak, Ph.D.
Review Chemist, HFD-540

cc:
Org. NDA 18-713/S-017
HFD-540/Division File
HFD-540/PM/Cross
HFD 540/Biopharm/Mainigi
HFD-540/Chem/Gautambasak
HFD-540/TL/DeCamp
HFD-830/DivDir/Chen
R/D Init by: TEAMLEADER

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 18713
5017

/s/

Mamta Gautam-Basak
3/22/01 12:33:51 PM
CHEMIST

PDUFA goal date 7/23/01

Wilson H. DeCamp
3/22/01 12:43:18 PM
CHEMIST
concur with review; AP letter may be prepared

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

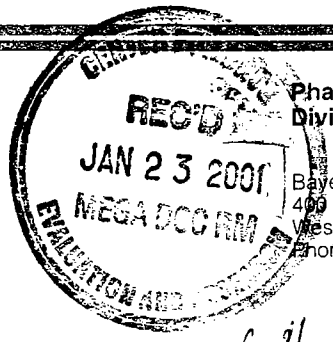
18-713/S-017

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA NO. 18-713 REF. NO. 017

NDA SUPPL FOR SCM

Bayer



Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

January 22, 2001

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V (HFD-540)
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850

jwd
2/26/01

Re: NDA 18-713 Mycelex® (clotrimazole) Troche
Special Supplement – Changes Being Effected in 30 Days

Dear Dr. Wilkin,

The Bayer Corporation, Pharmaceutical Division is submitting this supplement per 21 CFR 314.70 to NDA 18-713, Mycelex® (clotrimazole) Troche. The purpose of this supplement is to provide the alternate drug substance manufacturing facility [redacted]

The drug substance, clotrimazole, is the subject of a Drug Master File [redacted] which was updated on December 21, 2000. This update included the appropriate information regarding [redacted] Also included, was the additional information per the Division's request in an Information Request Letter received by Bayer (dated September 20, 2000).

The submission of this additional manufacturing step was discussed with Dr. DeCamp, Dr. Basak, and Mr. Cross in a teleconference held on October 17, 2000. As requested by the Division, the following information has been provided:

Appendix 1: A copy of the cover letter of the amendment filed to [redacted]
Appendix 2: A comprehensive list of all NDAs and ANDAs affected by this change
Appendix 3: A comprehensive list of all the companies who are provided the clotrimazole drug substance from [redacted]
Appendix 4: A copy of the October 17, 2000 teleconference minutes

Bayer would be pleased to provide desk copies of the clotrimazole DMF to the Chemistry reviewers per your request.

ORIGINAL

Thank you for your attention to this supplement. If you have any questions regarding this submission please contact me at (203) 812-2112 or Mr. Arthur D. Edwards at (203) 812-2630.

Sincerely,

Robin M. Christoforides

Robin M. Christoforides
Assistant Director, Regulatory Affairs

Desk Copy: Frank Cross, Sr. Project Manager (Complete Submission)
Mamta Gautam-Basak, Chemistry Reviewer (Complete Submission)
Wilson DeCamp, Chemistry Reviewer (Complete Submission)

D.F

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-713/S-017

APR 6 2001

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

Attention: Andrew S. Verderame Deputy Director, Regulatory Affairs

Dear Mr. Verderame:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Mycelex (clotrimazole) Troche

NDA Number: 18-713

Supplement Number: S-017

Date of Supplement: January 22, 2001

Date of Receipt: January 23, 2001

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on March 24, 2001, 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,

for 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

cc:
Original NDA 18-713/S-017
HFD-540/Div. Files
HFD-540/CSO/F. Cross Jr.

SUPPLEMENT ACKNOWLEDGEMENT