CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-713/S-014

Trade Name: Mycelex Troche 10 mg

Generic Name: clotrimazole

Sponsor: Miles Pharmaceuticals

Approval Date: October 7, 1999

Indications: For the local treatment of oropharyngeal candisis.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-713/S-014

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APPLICATION NUMBER:

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APPROVAL LETTER

Div file

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-713/S-014

OCT 7 1999

Bayer Corporation, Pharmaceutical Division
Attention: Andrew S. Verderame
Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Mr. Verderame:

Please refer to your supplemental new drug application dated April 7, 1999, received April 8, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mycelex (clotrimazole) Troche.

We acknowledge receipt of your submissions dated June 9 and September 1, 1999.

This supplemental new drug application provides for an alternate manufacturing site [redacted] clotrimazole [redacted].

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

Sincerely,

WHD 10/7/99

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

cc:
Archival NDA 18-713
HFD-540/Div. Files
HFD-540/Wilkin
HFD-540/Cross
HFD-540/Walker
HFD-540/Jacobs
HFD-540/Huene
HFD-540/Mainigi
HFD-540/Gautam-Basak 10/7/99
HFD-540/DeCamp
HFD-880/Bashaw
HFD-095/DDMS-IMT
HFD-830/Chen
DISTRICT OFFICE

Drafted by: whd/10/7/99
filename: 18713S14.AP

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-713/S-014

LABELING

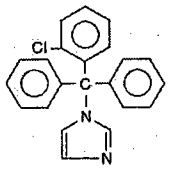
MYCELEX®

(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-014

CHEMISTRY REVIEW(S)

Div file

OCT 7 1999

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

NDA #: 18-713 **REVIEW #: 1** **REVIEW DATE: 10/07/99**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SCM-014	07-APR-99	08-APR-99	
BC	09-JUN-99	10-JUN-99	22-JUN-99
BC	01-SEP-99	03-SEP-99	13-SEP-99

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:	/ —— /
Product Number:	
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: / ——

SUPPORTING DOCUMENTS (if applicable): / —— / March 30, 1999

REMARKS/COMMENTS:
The supplemental new drug application provides for an alternate manufacturing site / —— / for clotrimazole / —— / The approved manufacturing site for drug substance is located / —— / Per amendment dated September 1, 1999, / ——
Review of the / —— submission dated 3/30/99 was completed and found to be acceptable. There are no significant changes in the manufacturing process and/or specifications of the drug substance produced at the proposed site. The drug substance is produced and tested by the approved specifications and methods.

The cGMP status of the proposed manufacturing site is acceptable per EER report attached.

CONCLUSIONS & RECOMMENDATIONS:

Recommend approval.

M G Basak 10/7/99

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

cc:
Org. NDA 18-713/S-014
HFD-540/Division File
HFD-540/PM/Cross
HFD 540/Biopharm/Mainigi
HFD-540/Chem/Gautambasak
HFD-540/TL/DeCamp W/S 10/7/99
HFD-830/DivDir/Chen
R/D Init by: TEAMLEADER

1 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 18-713
S014

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 18713/014**
Priority: **3S** Org Code: **540**
Stamp: **08-APR-1999** Regulatory Due: **08-OCT-1999**
Action Goal: District Goal: **03-SEP-1999**
Applicant: **BAYER**
400 MORGAN LANE
WEST HAVEN, CT 065164175
Brand Name: **MYCELEX (CLOTRIMAZOLE) TROCHE**
Established Name:
Generic Name: **CLOTRIMAZOLE**
Dosage Form: **TRO (TROCHE)**
Strength: **10 MG**

FDA Contacts: **F. CROSS JR (HFD-540) 301-827-2023 , Project Manager**
M. GAUTAM BASAK (HFD-540) 301-827-2074 , Review Chemist
W. DECAMP II (HFD-540) 301-827-2041 , Team Leader

Overall Recommendation:

ACCEPTABLE on 07-OCT-1999 by S. ADAMS (HFD-320) 301-594-0095

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **07-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: [redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-713/S-014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DF

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18713/S-014

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

APR 12 1999

Attention: Andrew S. Verderame
Associate Director, Regulatory Affairs

Dear Mr. Verderame:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Mycelex (clotrimazole) Troche

NDA Number: 18713

Supplement Number: S-014

Date of Supplement: April 7, 1999

Date of Receipt: April 8, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on June 7, 1999 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,

4/9/99

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 18713/S-014
HFD-540/Div. Files
HFD-540/CSO/F. Cross

SUPPLEMENT ACKNOWLEDGEMENT