CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-713/S-004

Trade Name: Mycelex Troche 10 mg

Generic Name: clotrimazole

Sponsor: Miles Pharmaceuticals

Approval Date: June 3, 1987

Indications: For the local treatment of oropharyngeal candisis.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-713/S-004

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Reviews / Information Included in this NDA Review.

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APPLICATION NUMBER:

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APPROVAL LETTER

4.1

JUN 05 1987

NDA 18-182/S-007
18-230/S-007
18-713/S-004
19-069/S-004

Mr. Charles F. Rayner
Manager, Regulatory Compliance
Miles Pharmaceuticals
400 Morgan Lane
West Haven, Connecticut 06516

Dear Mr. Rayner:

Reference is made to your supplemental New Drug Applications dated December 22, 1986 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mycelex-G (clotrimazole) Tablets 100 mg (NDA 18-182), Mycelex-G (clotrimazole) Cream 1% (NDA 18-230), Mycelex (clotrimazole) Troche 10 mg (NDA 18-713), and Mycelex - G (clotrimazole) Tablets 500 mg (NDA 19-069).

The supplemental applications provide for the referencing of all requisite information for the synthesis of the drug substance including description, chemistry, manufacture, and controls into two DMF's:

It is understood that / , will be the primary supplier and / the alternate supplier.

We have completed the review of these supplemental applications and they are approved. Our previous letters detailed the conditions concerning the approval of the original applications.

Sincerely yours,

Edward Tabor, M.D.
Director
Division of Anti-Infective
Drug Products
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: BOS-DO
Orig NDA
HFN-815
HFN-815/CSO
HFN-815/ARCasola
HFN-815/MO
HFN-815/Wayland:gm 5/19/87
R/D init. by: ARCasola 5/19/87
Approve
0662c

ARC 5/22/87

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-713/S-004

LABELING

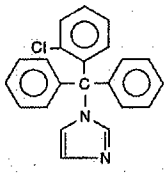
MYCELEX®

(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

alza TM
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-004

CHEMISTRY REVIEW(S)

NDA SUPPLEMENT REVIEW

CHEMIST's REVIEW

1. ORGANIZATION
DAIDP

2. NDA NUMBER 18-182
18-713,18-230, &19-069

3. NAME AND ADDRESS OF APPLICANT (CITY AND STATE)
Miles Pharmaceuticals
400 Morgan Lane
West Haven, CT 06516

4. AF NUMBER

5. SUPPLEMENT(s)

NUMBER(s)	DATE(s)
18-182/S-007	12-22-86
18-230/S-007	reassigned
18-713/S-004	to this
19-069/S-004	Chem. 4/87

6. NAME OF DRUG
Mycelex

7. NONPROPRIETARY NAME
clotrimazole

8. SUPPLEMENT(s) PROVIDES FOR: the placing of all information on the synthesis of the NDS into the DMF's of the two suppliers,

9. AMENDMENTS AND OTHER (REPORTS, etc) DATES

10. PHARMACOLOGICAL CATEGORY
Antifungal

11. HOW DISPENSED
X Rx OTC

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM(s)
Vaginal Tablets oral troche
Vaginal Cream

14. POTENCY(ies)
vag tab. 100 mg vag. tab. 500 mg
vag. crm. 1% oral troche 10 mg

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS

CURRENT		REVIEWED	
Yes	No	Yes	No

17. COMMENTS
The primary reason for removing this information from the NDAs and placing it in master files is for efficient ease of handling when any of the subject processes are amended.

Mr. Charles Rayner is the authorized agent responsible for the submission of the master files.

18. CONCLUSIONS AND RECOMMENDATIONS:
The amendments may be approved. Draft letter is attached.

cc: ORIG NDA
HFN-815 HFN-815/CSO
HFN-815/MO HFN-815/Wayland: gm 5/19/87
R/D initialed by: ARCasola 5/19/87 ARC 5/22/87

19. NAME	REVIEWER SIGNATURE	DATE COMPLETED
Lola G. Wayland		5-19-87

DISTRIBUTION ORIGINAL JACKET REVIEWER DIVISION FILE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-713/S-004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Miles

MILES

Miles Pharmaceuticals
Division of Miles Laboratories, Inc.

400 Morgan Lane
West Haven, Connecticut 06516
(203) 934-9221

NDA NO. 18713 REF. NO. 5004

NDA SUPPL FOR CN

December 22, 1986

Edward Tabor, M.D., Director
Anti-Infective Drug Division
Center for Drugs and Biologics (HFN-823)
Attention: DOCUMENT CONTROL ROOM 12B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
JAN 06 1987
HFN-815
CDB - DAIDP

Re: NDA 18-713 MYCELEX® (clotrimazole) Troche 10 mg

Dear Dr. Tabor:

Miles Pharmaceuticals hereby submits a supplement to the above referenced NDA. The purpose of the supplement is to reference two separate Drug Master Files (DMF's). [redacted]

These DMF's contain all the requisite information [redacted] clotrimazole, including the description, chemistry, manufacture and controls. The DMF's have been submitted to the FDA's Drug Information Service Branch (HFN-84). Numbers have not yet been assigned to these DMF's.

I, Charles Rayner have been appointed as the authorized agent responsible for the submission of [redacted]. I will act as a liasion; all future correspondence should be addressed to my attention.

The official letters appointing me as an agent from [redacted] are included in this submission as well as in the DMF's. Statement of Commitment letters are included from [redacted] that they will conform to the specifications listed in the Drug Master Files. These DMF's will be maintained in accordance with 21 CFR, 314.420. Also included are letters of authorization to allow FDA to reference these DMF's on behalf of Miles Pharmaceuticals.

We would like to name [redacted]

There are no major changes in ' —— ' manufacture or control information contained in the DMF's from that previously submitted in the original NDA submission. The data has been updated to current format.

Since all the required information describing the ' —— ' clotrimazole is contained in the DMF's, please now disregard or remove this data originally submitted in the NDA's.

Sincerely,

Charles F. Rayner

Charles F. Rayner
Manager, Regulatory Compliance

CAS/gsm
attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date JAN 19 1987

NDA No. 19-713

Miles Pharmaceuticals
Division of Miles Laboratories, Inc.
400 Morgan Lane
West Haven, CT 06516

Attention: Charles F. Rayner
Manager, Regulatory Compliance

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Mycelex (clotrimazole) Troche 10 mg.

NDA Number: 19-713

Supplement Number: S-004

Date of Supplement: December 22, 1986

Date of Receipt: January 6, 1987

All communications concerning this NDA should be addressed as follows:

Center for Drugs and Biologics, HFN-815
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Center for Drugs and Biologics

cc:
NDA File
HFN-815 File
CSO File

FORM FDA 3217d (7/84)

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