CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 64142

Trade Name Nystatin Oral Suspension USP, 100,000 Units/ml

Generic Name Nystatin Oral Suspension USP, 100,000 Units/ml

Sponsor UDL Laboratories, Inc.
## CONTENTS

<table>
<thead>
<tr>
<th>Item</th>
<th>Included</th>
<th>Pending Completion</th>
<th>Not Prepared</th>
<th>Not Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tentative Approval Letter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approvable Letter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Printed Labeling</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Review(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA/FONSI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacology Review(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statistical Review(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopharmaceutics Review(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioequivalence Review(s)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administrative Document(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correspondence</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 64142

APPROVAL LETTER
UDL Laboratories, Inc.
Attention: Dina Kostakis
7265 Ulmerton Road
Largo, FL 33771

Dear Madam:

This is in reference to your abbreviated new drug application dated December 5, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nystatin Oral Suspension USP, 100,000 Units/mL. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997. Reference is also made to your amendments dated September 25, 1997; and March 9, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Nystatin Oral Suspension USP, 100,000 Units/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Mycostatin® Oral Suspension, 100,000 Units/mL, of Apothecon, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.
Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64142

FINAL PRINTED LABELING
Nystatin Oral Suspension, USP
AADA 64-142
UDL Laboratories, Inc.

**Container Label**

NDC 51079-307-0

**Tray (Carton) Label**


NYSTATIN ORAL SUSPENSION, USP
500,000 Units/5 ml

SHAKE WELL
10 Unit-Dose Caps of 5 ml each
Each ml for oral administration contains 500,000 units of nystatin. Alcohol (not more than 1.5%). Each ml contains the following: water for injection, sodium carboxymethylcellulose, sodium dihydrogen phosphate, flavoring, glycerin, lecithin, sodium hydroxide, propylene glycol, sodium chloride, sucrose, and water for injection.

USUAL DOSAGE: See package insert for dosage information.
CAUTION: Federal law prohibits dispensing without prescription.
Keep this and all drugs out of the reach of children.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from freezing.
See bottom of container for lot number and expiration date.
UDL Laboratories, Inc.
Rockford, Ill. 61103
NYSTATIN
ORAL SUSPENSION, USP

DESCRIPTION
Nystatin is an antifungal polyene antibiotic obtained from Streptomyces noursei.
The structural formula is:

![Structural formula of nystatin]

Each mL, for oral administration, contains 100,000 units of nystatin. Alcohol (not more than 1% v/v). In addition, each mL contains the following inactive ingredients: carboxymethylcellulose sodium, dibasic sodium phosphate, flavoring, glycerin, methylparaben, monobasic sodium phosphate, propylparaben, purified water, sorbitan sodium and sucrose (50% w/v).

CLINICAL PHARMACOLOGY
Pharmacokinetics
Gastrointestinal absorption of nystatin is insignificant. Most orally administered nystatin is passed unchanged in the stool. In patients with renal insufficiency receiving oral therapy with conventional dosage form, significant plasma concentrations of nystatin may occasionally occur.

Microbiology
Nystatin is both fungistatic and fungicidal in vitro against a wide variety of yeasts and yeast-like fungi. Candida albicans demonstrates no significant resistance to nystatin in vitro on repeated subculture in increasing levels of nystatin; other Candida species become quite resistant. Generally, resistance does not develop in vivo. Nystatin acts by binding to sterols in the cell membrane of susceptible Candida species with a resultant change in membrane permeability allowing leakage of intracellular components. Nystatin exhibits no appreciable activity against bacteria, protozoa, or viruses.

INDICATIONS AND USAGE
Nystatin oral suspension is indicated for the treatment of candidiasis in the oral cavity.

CONTRAINDICATIONS
The preparation is contraindicated in patients with a history of hypersensitivity to any of its components.

PRECAUTIONS
General
This medication is not to be used for the treatment of systemic mycoses. Discontinue treatment if sensitization or irritation is reported during use.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have been performed to evaluate carcinogenic potential. There are also no studies to determine mutagenicity or whether this medication affects fertility in males or females.

Pregnancy: Teratogenic Effects
Category C: Animal reproduction studies have not been conducted with nystatin oral suspension. It is also not known whether nystatin oral suspension can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nystatin oral suspension should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether nystatin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nystatin is administered to a nursing woman.

Pediatric Use
See DOSAGE AND ADMINISTRATION.
ADVERSE REACTIONS
Nystatin is well tolerated even with prolonged therapy. Oral irritation and sensitization have been reported. (See PRECAUTIONS: General.)
Gastrointestinal: Diarrhea (including one case of bloody diarrhea), nausea, vomiting, gastrointestinal upset/disturbances.
Dermatologic: Rash, including urticaria has been reported rarely. Stevens-Johnson syndrome has been reported very rarely.
Other: Tachycardia, bronchospasm, facial swelling, and nonspecific myalgia have also been rarely reported.

OVERDOSE
Oral doses of nystatin in excess of five million units daily have caused nausea and gastrointestinal upset. There have been no reports of serious toxic effects or superinfections (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

DOSAGE AND ADMINISTRATION
INFANTS: 2 ml (200,000 units of nystatin) four times daily (in infants and young children, use dropper to place one-half of dose in each side of mouth and avoid feeding for 5 to 10 minutes).
NOTE: Limited clinical studies in premature and low birth weight infants indicate that 1 ml four times daily is effective.

CHILDREN AND ADULTS: 4-6 ml (400,000 to 600,000 units nystatin) four times daily
(one-half of dose in each side of mouth). The preparation should be retained in the mouth as long as possible before swallowing.
Continue treatment for at least 48 hours after perianal symptoms have disappeared and cultures demonstrate eradication of Candida albicans.
Shake well before use.

HOW SUPPLIED
Nystatin Oral Suspension, USP is available as a cherry flavored, light creamy yellow, ready-to-use suspension containing 100,000 units nystatin per mL. It is supplied as follows:
NDC 51079-307-10 — Unit dose cups of 5 mL in cartons of 50
(5 trays of 10 unit dose cups each)

Storage
Store at controlled room temperature 15°C-30°C (59°F-86°F). Avoid freezing.
Caution: Federal law prohibits dispensing without prescription.

UDL Laboratories, Inc. Rockford, IL 61103

FP912 R2 Rev. 1/97
1. CHEMIST'S REVIEW NO. #7 (revised)

2. ANDA #64-142

3. NAME AND ADDRESS OF APPLICANT

UDL Laboratories, Inc.
Attention: Dina Kostakis
7265 Ulmerton Road
Largo, FL 33771

Phone: 813-530-1633
Fax: 813-531-5427

4. LEGAL BASIS FOR SUBMISSION

21 CFR §449.150b
Reference drug: MYCOSTATIN® ORAL SUSPENSION (Nystatin Oral Suspension, USP) manufactured by E.R. Squibb & Sons, Inc. (Apothecon is the current holder)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Nystatin Oral Suspension, USP

8. SUPPLEMENT(s) PROVIDE[s] FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Original Submission: 12/5/94
Acknowledgment: 1/11/95
N/A letter (MINOR): 5/12/95
Amendment: 6/27/95
Amendment 4/4/97 to N/A letter (MAJOR) 10/6/95
Amendment 9/18/97 to N/A letter (FACSIMILE) 8/21/97
Amendment 9/25/97 (Telephone Amendment for BIO issue)
Amendment 11/11/97 to N/A letter (MINOR) 10/23/97
Amendment 3/9/98 to N/A letter (FACSIMILE) 1/12/98
10. PHARMACOLOGICAL CATEGORY: Antifungal
11. Rx or OTC: Rx
12. RELATED IND/NDA/DMF(s):
13. DOSAGE FORM: Oral Suspension
14. POTENCY:
   500,000 u/5 mL
   (10 mL package withdrawn in Amendment 6/27/95)
15. CHEMICAL NAME AND STRUCTURE:
   C₁₁₇H₂₃NO₃, MW = 926.13
   (see CR #1)
16. RECORDS AND REPORTS: N/A
17. COMMENTS:
   A. In Amendment 4/4/97, to answer N/A (MAJOR) letter 10/6/95 (concentration of
   exceeds the previously approved in a pharmaceutical dosage form for the same route of administration), Firm has
   reformulated the Nystatin Oral Suspension by removing from the originally proposed drug product and increasing the parabens from
   methylparaben and propylparaben to and , respectively. Firm submits revised chemistry, manufacturing, controls and labeling
   information in the amendment.
   CR #4 supersedes the previous reviews unless otherwise indicated.
B. Amendment 3/9/98 Firm answers in order:

Q1. On page 414 (Product Reconciliation Form in the batch records) of your Amendment dated 4/4/97, under Packaging Accountability, we note that "Avg. Fill Volume" is listed as __________. It is not clear how this value was obtained since the __________ was set at __________ and the record on page 404 verified the limits. Please explain.

A1. The Average Fill Volume and Average Delivery Volume are two different processes within the filling operation. Average Fill Volume is the amount of the product that is placed within the unit dose cup at the filling stage. Average Delivery Volume is the amount of the product that is delivered from the unit dose cup. Average Delivery Volume obtained for lot 606046 ranged from __________ and fall within the established specifications of __________. The calculations are provided.

Q2. Your samples have been tested by our laboratory and found to have a potency which exceeds the upper limit:

Results:

- **Nystatin (100,000 u/mL, I.C.)**
  - Container 5 - 139,000
  - Container 6 - 141,000
  - Container 7 - 133,000
  - Avg 3 = 137,700 u/mL (137.7% of I.C.)

Potency limit: 90.0 - 130.0% (USP)

a. Our laboratory used one mL of sample from each container for the assay procedure. We are not certain how you prepared samples for the potency assay. Did you follow the same sample preparation procedure as described under UNIFORMITY OF DOSAGE UNITS on page 493 of the Amendment dated April 4, 1997? Please clarify.

b. Please comment on our laboratory findings.

A2. UDL used two different outside testing laboratories for assaying the potency of Lot #606046. Both laboratories show correlatable results within expected assay variability and the assay specification for Nystatin of 90.0 - 130.0% (USP). Results are
The laboratories conduct the test from a composite sample provided by UDL. The composite for finished product testing is prepared by UDL laboratories prior to sending to the outside testing laboratory. The composite is prepared by shaking well, a sufficient number of unit-dose cups, one at a time, and pouring the contents into a sample bottle for the composite. A portion of the same composite sample is used to perform the Uniformity of Dosage Unit and test for Uniformity of Dosage Unit.

Pirm comments that it is critical to perform ample shaking of the cup as well as pipet the sample immediately after shaking. Either one of these factors could contribute to a higher biased assay. UDL is willing to communicate with the FDA laboratory to discuss the test method and offer its assistance.

Comments:

1. The bulk supplier is acceptable per 5/15/98 recommendation (see report dated 6/11/98).

2. The finished product and stability specifications, and testing procedures have been revised to include dissolution testing according to the requested test parameters and specifications.

3. The additional samples sent by UDL in April 1998 are still under review. Since this is a compendial drug product, it does not need to be tested by our District Laboratories under current policy. Nystatin is absorbed very sparingly following oral administration, with no detectable blood levels when given in the recommended doses. Most of the orally administered nystatin is passed unchanged in the stool. It should not pose any safety issue even though our lab found the previous samples to exceed the potency limits (Avg. 137.7% of label claim; USP 90.0-130.0%).

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended

19. REVIEWER: Maria C. Shih
DATE COMPLETED: 3/16/98 (revised 6/11/98)