

**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.,**

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION 64142**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number      64142**

**APPROVAL LETTER**

JUN 25 1998

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 Apothecan, 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



6-25-98


**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      64142**

**FINAL PRINTED LABELING**

Container Label

NDC 51079-307-0



**NYSTATIN**  
**ORAL SUSPENSION, USP**  
500,000 Units/5 mL

Alcohol not more than 2%

SHAKE WELL

UDL Laboratories, Inc.  
Rockford, IL 61103



DELIVERS  
5 mL

JUN 25 1998

APPROVED

Tray (Carton) Label

NDC 51079-307-11 JUN 25 1998



**NYSTATIN**  
**ORAL SUSPENSION, USP**  
500,000 Units/5 mL

SHAKE WELL

10 Unit-Dose Cups of 5 mL each

Each mL, for oral administration, contains 100,000 units of nystatin. Alcohol (not more than 2% v/v). In addition, each mL contains the following inactive ingredients: benzaldehyde, carboxymethylcellulose sodium salt, sodium phosphate, flavoring, glycerin, methylparaben, monobasic sodium phosphate, propylparaben, purified water, saccharin sodium and sucrose (50% w/v).

APPROVED

**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, IL 61103

FP909



FP912 R2

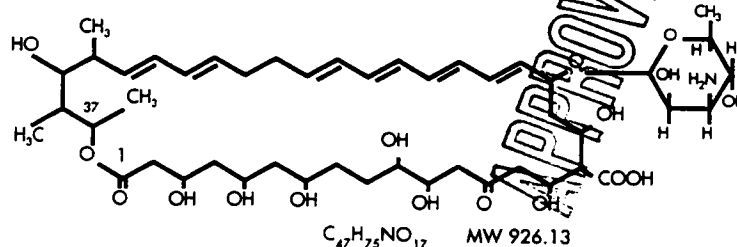
# NYSTATIN ORAL SUSPENSION, USP

JUN 25 1961

## DESCRIPTION

Nystatin is an antimycotic polyene antibiotic obtained from *Streptomyces noursei*.

The structural formula is:



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, saccharin 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 also have been 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.

012A



#### 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.

#### OVERDOSAGE

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 perioral 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°-30°C (59°-86°F). Avoid freezing.

**Caution:** Federal law prohibits dispensing without prescription.

 UDL Laboratories, Inc.  
Rockford, IL 61103

FP912 R2  
Rev. 1/97

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      64142**

**CHEMISTRY REVIEW(S)**

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

$C_{47}H_{75}NO_{17}$  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, l.c.)  
Container 5 - 139,000  
Container 6 - 141,000  
Container 7 - 133,000  
Avg 3 = 137,700 u/mL (137.7% of l.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

provided.

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.

Firm 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)