

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-003

CHEMISTRY REVIEW(S)



NDA 22-003

NDA 22-027

NOXAFILTM

(posaconazole)

Oral Suspension, 40 mg/mL

Schering Corporation

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ONDQA

Division of Pre-Marketing Assessment II

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CHEMISTRY REVIEW



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*Appears This Way
On Original*



Chemistry Review Data Sheet

Telephone: (908) 298-4000

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NOXAFIL™
- b) Non-Proprietary Name (USAN): posaconazole
- c) Code Name/# (ONDC only): SCH56592
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: NDA 22-003 Priority
NDA 22-027 Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antifungal Agent - Systemic

11. DOSAGE FORM: Oral Suspension

12. STRENGTH/POTENCY: 40 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

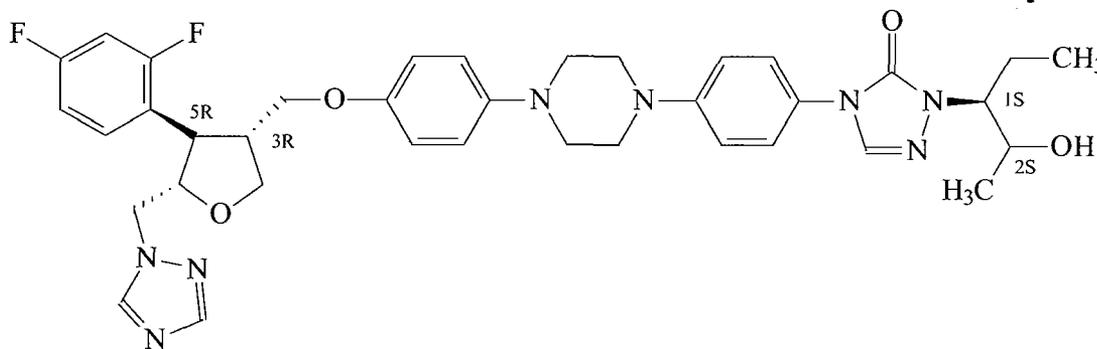
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet

IUPAC Name: 4-[4-[4-[4-[(3R,5R)-5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-yl)methyl]-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one

IUPAC Name (Alternate): 4-4-[4-(4-[(3R,5R)-5-(2,4-difluorophenyl)-5-(1H-1,2,4-triazol-1-yl)methyl]tetrahydro-3-furanyl]methoxyphenyl)piperazino]phenyl-1-[(1S,2S)-1-ethyl-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-5-one

CAS Index Name: D-threo-pentitol, 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-[(1S,2S)-1-ethyl-2-hydroxypropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)



Molecular Formula: $C_{37}H_{42}F_2N_8O_4$

Molecular Weight: 700.78

CAS: 171228-49-2

WHO Number: 7713

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|-------|------|--------|-----------------|-------------------|---------------------|-----------------------|----------|
| | IV | | | 1 | Adequate | 15-NOV-1996 | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 3 | Adequate | 12-APR-2004 | |

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Chemistry Review Data Sheet

Other codes indicate why the DMF was not reviewed, as follows:

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|--------------------------------------|---------------------|------------------------------------------------------------------------|
| Investigational New Drug Application | 51,316 (Aug., 1996) | Posaconazole Capsules, 50-, 100-mg |
| Investigational New Drug Application | 51,662 (Oct., 1996) | Posaconazole Oral Suspension, 40 mg/mL Posaconazole Tablets, 100-mg |

18. STATUS:

ONDC:

| CONSULTS/CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|------------------------------|-------------------------------------------|-------------|-------------------------|
| Biometrics | n/a | | |
| EES | Acceptable (See EES for Detail Report) | 31-MAY-2006 | J.D. Ambrogio (HFD-322) |
| Pharm/Tox | n/a | | |
| Biopharm | n/a | | |
| LNC | n/a | | |
| Methods Validation | n/a | | |
| DMETS | Labeling comments provided | 23-MAY-2006 | DMETS Staff |
| EA | Categorical exclusion acceptable | 19-JUN-2006 | M. Seggel |
| Microbiology | n/a | | |

The Chemistry Review for NDA 22-003 and NDA 22-027

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application, as amended, is recommended for approval from the chemistry, manufacturing and controls perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no recommendations for Phase 4 CMC commitments. The applicant will continue to monitor the stability of the drug substance and drug product.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product and drug substance are described in detail in _____ See _____

Posaconazole oral suspension, 40 mg/mL, is a white, _____ immediate release oral suspension formulation. It is comprised of _____ particles of posaconazole drug substance suspended in a _____ cherry-flavored vehicle. Inactive ingredients include polysorbate 80, simethicone, sodium benzoate _____ citrate _____ glycerin, glucose, cherry flavor, titanium dioxide, xanthan gum _____) and purified water. These excipients are commonly used in oral suspensions and other oral drug products. The manufacturing process involves the _____

The drug product is packaged in amber glass bottles with child-resistant _____ closures having a _____ closure liner. _____ bottle sizes are described in the NDA, _____ the 4-ounce presentation is proposed for the US market at this time.

Posaconazole oral suspension is a very stable suspension that settles very slowly and has good redispersibility. Posaconazole oral suspension also exhibits good chemical stability and physical stability.

Executive Summary Section

The product specification includes tests for assay, degradation, dissolution, viscosity and particle size.

Posaconazole drug substance, a triazole-containing antifungal agent, is prepared by a ~~process~~. It is structurally related to ketoconazole and itraconazole. Posaconazole has ~~one~~ chiral centers. The correct isomer is controlled by the method of synthesis and chiral HPLC.

~~Posaconazole~~ has good stability and degrades only under stress conditions. The drug substance specification includes tests for identity, assay and impurities that use both chiral and achiral HPLC methods.

B. Description of How the Drug Product is Intended to be Used

As originally submitted, NDA 22-003 provided for both a IFI prophylaxis indication and an OPC treatment indication. Subsequently, the application was administratively split into two separate applications, NDA 22-003 and NDA 22-027.

NDA 22-003: NOXAFIL (posaconazole) is indicated for prophylaxis of invasive fungal infections (IFI), including both yeasts and moulds, in patients, 13 years of age and older, who are at high risk of developing these infections, such as hematopoietic stem cell transplant (HSCT) recipients or those with prolonged neutropenia.

Typical dosing is 200 mg (5 mL) three times a day; the duration of therapy is based on recovery from neutropenia or immunosuppression.

NDA 22-027: NOXAFIL (posaconazole) is indicated for the treatment of oropharyngeal candidiasis, including infections refractory to itraconazole and fluconazole.

Typical dosing is 100 mg (2.5 mL) once a day for thirteen days, after a loading dose of 200 mg (5 mL) on the first day. For refractory oropharyngeal candidiasis, 400 mg (10 mL) twice a day. Duration of therapy should be based on the severity of the patient's underlying disease and clinical response.

The drug is dosed with a 5-mL ~~measuring~~ spoon that is provided with the drug product.

Executive Summary Section

The drug product is physically and chemically stable. Stability data support the proposed expiration dating period of 24 months stored at 25°C/60% RH with excursions permitted to 15-30°C (see USP Controlled Room Temperature).

C. Basis for Approvability or Not-Approval Recommendation

From the chemistry, manufacturing and controls perspective the application, as amended, can be approved.

Adequate information is provided regarding the chemistry, manufacturing and controls of the drug substance and drug product. The requirements of 21 CFR 314.50(d)(1) have been adequately met by the applicant. Drug substance and drug product specification provide assurance of the identity, strength, quality, purity and bioavailability of the product.

The drug substance and drug product manufacturing facilities have Acceptable cGMP status (see EES).

III. Administrative**A. Reviewer's Signature**

{see electronic signature page}

B. Endorsement Block

{see electronic signature page}

C. CC Block

{see dfs}

8 Page(s) Withheld

8 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry-

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mark Seggel
6/21/2006 11:29:32 AM
CHEMIST

Elaine Morefield
6/21/2006 01:36:06 PM
CHEMIST