

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-027**

**PHARMACOLOGY REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-003/22-027  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: 12/21/2005 and 2/23/2006  
PRODUCT: NOXAFIL<sup>®</sup> (posaconazole) Oral Suspension  
INTENDED CLINICAL POPULATION: Patients with Invasive fungal infections  
SPONSOR: Schering Corporation  
2000 Galloping Hill Rd  
Kenilworth NJ 07033  
  
DOCUMENTS REVIEWED: \_\_\_\_\_  
REVIEW DIVISION: Division of Special Pathogen and Transplant  
Products (HFD-590)  
PHARM/TOX REVIEWER: Owen McMaster, PhD  
PHARM/TOX SUPERVISOR: William Taylor, PhD  
DIVISION DIRECTOR: Renata Albrecht, MD  
PROJECT MANAGER: Kristen Miller, PharmD

Date of review submission to Division File System (DFS): June 20, 2006

## ***EXECUTIVE SUMMARY***

### **I. Recommendations**

#### **A. Recommendation on approvability.**

There are no toxicology findings that would preclude the approval of posaconazole for serious fungal infections.

#### **B. Recommendation for nonclinical studies**

No additional toxicology studies are being recommended at this time

#### **C. Recommendations on labeling**

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

No drug-related neoplasms were recorded in rats or mice treated with posaconazole for two years at doses below the maximum tolerated dose. In a two-year carcinogenicity study, rats were given posaconazole orally at doses up to 20 mg/kg (females), or 30 mg/kg (males). These doses are equivalent to 3.9 or 3.5 times the clinical dose of 400 mg BID (400 mg BID regimen), respectively, based on steady-state AUC in healthy volunteers administered a high-fat meal. In the mouse study, mice were treated at oral doses up to 60 mg/kg/day or 4.8 times the 400 mg BID regimen.

Posaconazole was not genotoxic or clastogenic when evaluated in bacterial mutagenicity (Ames) assays, a chromosome aberration study in human peripheral blood lymphocytes, a Chinese hamster ovary cell mutagenicity study, and a mouse bone marrow micronucleus study.

Posaconazole had no effect on fertility of male rats at a dose up to 180 mg/kg (1.7 x 400 mg BID regimen based on steady-state plasma concentrations in healthy volunteers) or female rats at a dose up to 45 mg/kg (2.2 x the 400 mg BID regimen).

### **Pregnancy Category C**

Posaconazole has been shown to cause skeletal malformations (cranial malformations and missing ribs) in rats when given in doses  $\geq 27$  mg/kg ( $\geq 1.4$  times the 400 mg BID regimen based on steady-state plasma concentrations of drug in healthy volunteers). The no-effect dose for malformations in rats was 9 mg/kg, which is 0.7 times the 400 mg BID regimen. No malformations were seen in rabbits at doses up to 80 mg/kg. In the rabbit, the no-effect dose was 20 mg/kg, while high doses of 40 mg/kg and 80 mg/kg, 2.9 or 5.2 times the 400 mg BID regimen, caused an increase in resorptions. In rabbits dosed at 80 mg/kg a reduction in body weight gain of females and reduction in litter size was seen. There are no adequate and well-controlled studies in pregnant women. Posaconazole

should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

## **Nursing Mothers**

Posaconazole is excreted in milk of lactating rats. The excretion of posaconazole in human breast milk has not been investigated. NOXAFIL should not be used by nursing mothers unless the benefit to the mother clearly outweighs the potential risk to the infant.

## **II. Summary of nonclinical findings**

### **A. Brief overview of nonclinical findings**

The toxicology studies conducted using posaconazole include oral mouse and rat studies (up to 2 years dosing), and dog and monkey studies (up to 12 months of dosing). Genetic toxicology, reproductive toxicology and special toxicology studies have also been performed.

Toxic effects include phospholipidosis (including neurophospholipidosis in dogs), vasculitis, disseminated intravascular coagulation, adrenal gland hyperplasia, spermatic giant cells, focal tubular atrophy of the testes and/or hypoplasia or atrophy of the prostate gland, ovarian stromal hyperplasia, uterine atrophy, increased heart weight and focal myocarditis

Pregnant females treated with posaconazole experienced abortions, dystocia, increased resorptions and maternal toxicity. Pups showed exencephaly, protruding tongue, anasarca, decreased fetal body weights, incomplete or reduced ossification of bones, absence of ossification of bones and microphthalmia. Adverse effects were observed as low as 0.5 times the proposed clinical dose based on body surface area comparisons.

Posaconazole did not demonstrate the potential to induce genotoxicity when studied using the bacterial reverse mutation tests (using strains of *Salmonella typhimurium* (*S. typhimurium*) and *Escherichia coli* (*E. coli*) to detect point mutations), chromosome aberration studies in cultured whole lymphocytes, and Chinese Hamster Ovary model of the HGPRT locus and mouse micronucleus test.

No evidence of carcinogenicity was observed at doses below the MTD. At doses above the MTD there were benign and malignant adrenal tumors in rats.

### **Phospholipidosis**

Posaconazole has been studied in rats (up to two years), mice (up to two years), dog (up to one year), monkeys (up to one year) and rabbits. Phospholipidosis has been detected in all species exposed to posaconazole and is generally characterized by

appearance of vacuolated cells of the monocyte/macrophage family. The cytoplasm of these cells contains masses that resemble plasma membrane. Posaconazole is thought to inhibit lysosomal phospholipases, thereby inhibiting the recycling of plasma membranes. The drug may also act like a number of other cationic amphiphilic compounds by inserting itself into the plasma membrane and disturbing turnover.

Phospholipidosis is most often detected in the lung, spleen, thymus, lymph nodes, liver, bone marrow, adrenal gland, pituitary, ovaries and skin. The thalamus, medulla, spinal cord and intestinal ganglia are also affected in posaconazole treated dogs.

Neuronal phospholipidosis was first observed in dogs in a twelve-month study. This consisted of vacuolation of neurons in thalamus, enlargement of axons of medulla, vacuolation of ganglia in small intestines and enlargement of axons of the spinal cord. Dogs treated for six months showed similar findings, though less frequently. Posaconazole was studied in dogs and monkeys in an attempt to determine the onset, functional effects and reversibility of the neuronal phospholipidosis. Animals were subjected to a number of neurological examinations. These included behavior, posture, gait, facial symmetry, muscle tone, patellar reflex, brainstem auditory evoked potentials, visual evoked potentials, somatosensory evoked potentials and peripheral nerve responses. No neuronal phospholipidosis was observed in the monkey. No functional consequences were observed in either species using the testing described above.

Phospholipidosis is generally thought to be without functional consequences even when observed in many tissues. In fact, rats experiencing amiodarone-induced lung phospholipidosis seem to be protected from the toxic effects of intratracheal silica (Environ. Health Perspec **102**:327-378). Phospholipidosis was generally ameliorated after a drug-free period, but in some cases the changes were not completely reversed at the end of a three month drug-free study period. Phospholipidosis is not unique to posaconazole and is seen with other azoles such as itraconazole. It is also a well known feature of cationic amphiphilic compounds such as amiodarone, fluoxetine, imipramine and gentamicin.

**APPEARS THIS WAY  
ON ORIGINAL**

## DRUG HISTORY

**NDA numbers:** \_\_\_\_\_

**Review number:** 1

**Sequence number:** 000

**Date:** 5/12/2004

**Information to sponsor:** Yes

**Sponsor:** Schering Corporation 2000 Galloping Hill Rd, Kenilworth NJ 07033

**Reviewer name:** Owen McMaster, PhD

**Division name:** Division of Special Pathogen and Transplant Products

**HFD-590**

**Review completion date:** May 24, 2006

### Drug:

Trade name: NOXAFIL®

Generic name: posaconazole

Code name: SCH56592

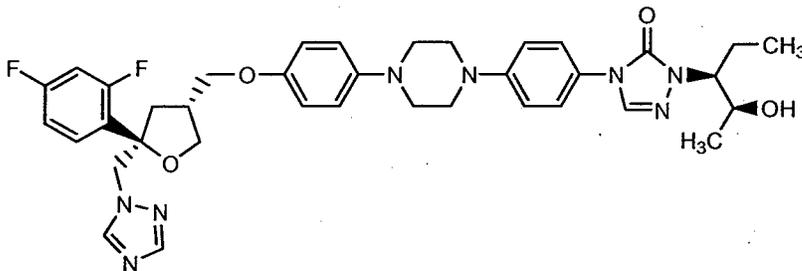
Chemical name: 4-[4-[4-[4-[[[(3R,5R)-5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one

CAS registry number:

Molecular formula: C<sub>37</sub>H<sub>42</sub>F<sub>2</sub>N<sub>8</sub>O<sub>4</sub>

Molecular weight: 700.8

Structure



**Related INDs:** 51,316 and 51,662

**Related NDA:** \_\_\_\_\_

**Drug class:** Triazole antifungal

**Indications:** NDA 22-003: Prophylaxis of invasive fungal infections

NDA 220-27: Oropharyngeal candidiasis

**Clinical formulation:** Posaconazole oral solution contains posaconazole (40 mg/ml), polysorbate \_\_\_\_\_, simethicone \_\_\_\_\_, sodium benzoate \_\_\_\_\_, sodium citrate dehydrate \_\_\_\_\_, citric acid monohydrate \_\_\_\_\_, glycerin, \_\_\_\_\_, xanthum gum \_\_\_\_\_, liquid glucose \_\_\_\_\_, titanium dioxide \_\_\_\_\_, artificial cherry flavor \_\_\_\_\_, and purified water \_\_\_\_\_.

**Route of administration:** Oral

**Toxicology Review**

NDA 22-003

No new Pharmacology or Toxicology studies were submitted with NDA 22-003. The applicant is meeting the regulatory requirement for Pharmacology and Toxicology studies for this NDA.

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NDA 22-027

No new Pharmacology or Toxicology studies were submitted with NDA 22-027. The applicant is meeting the regulatory requirement for Pharmacology and Toxicology studies for this NDA.

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/s/

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