CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-966**

CHEMISTRY REVIEW(S)

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-966

CHEMISTRY REVIEW #: 1 **DATE REVIEWED:** December 8, 1998

SUBMISSION	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	April 27, 1998	April 29, 1998	April 30, 1998
Amendment	August 24, 1998	August 25, 1998	September 1, 1998
Amendment	October 1, 1998	October 2, 1998	October 7, 1998

NAME & ADDRESS OF SPONSOR: Janssen Research Foundation
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

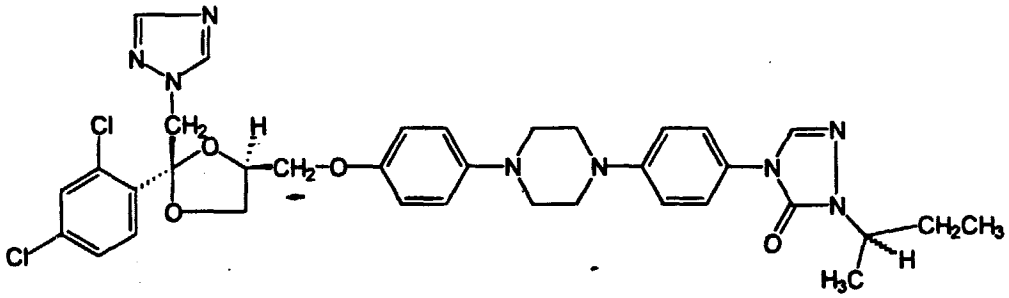
REPRESENTATIVE: Donna Ohye, Director, Regulatory Affairs
(609) 730-3396

DRUG PRODUCT NAME:

Proprietary:	SPORANOX® (itraconazole) Injection
Nonproprietary:	Itraconazole
Code Name/#:	R051211

PHARMACOLOGICAL CATEGORY: Antifungal
INDICATION: Treatment of blastomycosis, histoplasmosis and aspergillosis in immunocompromised and non-immunocompromised patients.
DOSAGE FORM/STRENGTH: Injection, 10 mg/mL (unit dose 20 mL)
ROUTE OF ADMINISTRATION: Intravenous infusion

CHEMICAL NAME/STRUCTURAL FORMULA: (±)-1-[(*RS*)-*sec*-butyl]-4-*p*-[4-*p*-[[(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one



Molecular Formula: $C_{35}H_{38}Cl_2N_8O_4$ **Molecular Weight:** 705.64 **CAS:** 84625-61-6

SUPPORTING DOCUMENTS: NDA 20-083, 20-657, 20-510, 16-366

DMF/Type	Title	LOA Date	Comments
		October 14, 1997	Reviewed
		May 14, 1997	
	Standard Microbiological Methods for the Flexible Container	April 6, 1998	Reviewed
	Hydroxypropyl Beta-Cyclodextrin	April 16, 1998	Reviewed
	Non-Clinical Pharmacology Studies on Hydroxypropyl-beta-cyclodextrin	None	
	Intermediate T001333	March 20, 1998	Current
	Intermediate T001330	March 20, 1998	Reviewed
	Itraconazole Drug Substance	March 23, 1998	Reviewed

RELATED DOCUMENTS:

Chemist's review of Sporanox® (itraconazole) for Injection
Chemist's review of NDA 20-657, Sporanox® (itraconazole) Oral Solution
Chemist's review of NDA 20-083, Sporanox® (itraconazole) Capsules

REMARKS/COMMENTS:

Sporanox® (itraconazole) Injection is a formulation of itraconazole in which hydroxypropyl-β-cyclodextrin (HP-β-CD) is employed as a solubilizing agent to maintain itraconazole in solution.

There are no CMC issues concerning bulk itraconazole. The drug is currently marketed as Sporanox® Capsules (NDA 20-083) and Oral Solution (NDA 20-657). CMC information concerning the drug substance is provided in the drug master files listed above. has been amended to add specifications for parenteral grade itraconazole. The amendment has been reviewed and is acceptable.

Itraconazole is nearly insoluble in water (< 1 mg/100 mL solution); thus, useful concentrations of itraconazole cannot be attained in water alone. During formulation development, studies were conducted in attempts to increase the itraconazole concentration to 10 mg/mL. Approaches tried

formulation is ultimately derived from that of Sporanox® (itraconazole) Oral Solution by

This page of the document contains confidential information that will not be included in the redacted portion of the document for the public to obtain.

With regard to the drug product, the specifications and methods in general are adequate. The sponsor should specify the sampling plan and number of samples used for the "volume in container" test. Numerical values should be reported for the sterility test, and specific USP references should be given. The RSD value for Accuracy of the HPLC method should be reported. The methods validation information is acceptable in general.

Stability data submitted (as amended) include

Data on three supportive batches manufactured by Janssen and packaged in amber-colored ampoules are also presented. The product appears to be quite stable upon storage when protected from light.

Possible degradation of HP-β-CD during storage has not been addressed.

Sporanox Injection is diluted with normal saline prior to administration. The method of mixing, volume ratio, speed and temperature of mixing and storage were examined. When the dilution is performed according to the directions provided, no precipitation is noted.

The compatibility of the itraconazole concentrate with infusion solutions, infusion materials was investigated with respect to particulate matter and assay of itraconazole. All studies indicated that the correct dose (90.0-110% of labeled amount) was delivered. The samples were not evaluated for assay of HP-β-CD.

Studies of the compatibility with comedication indicated that use of other products in the same container should be avoided.

Based upon the stability results for the registration batches (12 months), validation batches (3 months) and supportive data (18 months at 30°C) as well as a statistical analysis of the registration batch data, the company [redacted] as the expiration-dating period when stored in USP Type I siliconized glass ampoules at or below 25°C (77°F) and protected from light. An 18-month expiry period is reasonable considering the data submitted.

CONCLUSIONS & RECOMMENDATIONS:

The information on the chemistry, manufacturing and controls for NDA 20-966 has been provided and was deficient. The deficiencies were communicated to the sponsor on December 29, 1998. The company responded on March 12, 1999 and the response was adequate. From a CMC viewpoint, this application is now recommended for approved.

Deficiencies noted in the review, which were communicated to the sponsor, are outlined in the List of Chemistry Deficiencies and Comments. Please refer to Chemistry Review # 2 (in progress).

/S/

Gene W. Holbert, Ph.D., Review Chemist

Concurrence:
HFD-590/NSchmuff /S/ 3/18/99

cc:

Orig. NDA 20-966	HFD-590/R.Alivisatos	HFD-590/R.Kimzey
HFD-590/N.Schmuff	HFD-590/G.Holbert	HFD-590/K.Kumi
HFD-590/S.Bala	HFD-590/O.McMaster	File: N 20-966.000-