CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-966/S-001, S-003, S-004

20-657/S-004, S-005

ADMINISTRATIVE DOCUMENTS

PATENT AND EXCLUSIVITY INFORMATION

SPORANOX® (itraconazole) Oral Solution

Active Ingredient:	Itraconazole
Strength:	10 mg/mL
Trade Name:	SPORANOX®
Dosage Form:	Solution
Route of Administration:	Oral
NDA Number:	20-657
Approval Date:	February 21, 1997

Patent and Exclusivity Information:

U.S. Patent Number: Expiration Date:	4,267,179 June 23, 2000
Type of Patent:	Drug Substance
Name of Patent Owner:	Janssen Pharmaceutica, N.V. Beerse, Belgium
Agent of Patent Owner:	Audley A. Ciamporcero One Johnson & Johnson Plaza New Brunswick, NJ 08933-7003

U.S. Patent Number: Expiration Date:	5,707,975 January 13, 2015
Type of Patent:	Drug Product
Name of Patent Owner:	Janssen Pharmaceutica, N.V. Beerse, Belgium
Agent of Patent Owner:	Audley A. Ciamporcero One Johnson & Johnson Plaza New Brunswick, NJ 08933-7003

Patent and Exclusivity Information
SPORANOX® (itraconazole) Oral Solution
Page 2

U.S. Patent Number:	4,727,064
Expiration Date:	February 23, 2005
Type of Patent:	Drug Product
Name of Patent Owner:	United States of America, represented by the Department of Health and Human Services

The undersigned declares that Patents 5,707,975 and 4,727,064 cover the formulation, composition, and/or method of use of SPORANOX® (itraconazole) Oral Solution. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Date: April 24, 2000

Mary A. Appollina
Attorney for Applicant
Registered Patent Attorney
Registration No. 34,087

PATENT AND EXCLUSIVITY INFORMATION

SPORANOX® (itraconazole) Injection

Active Ingredient:	Itraconazole
Strength:	10 mg/mL
Trade Name:	SPORANOX®
Dosage Form:	Injection
Route of Administration:	Intravenous
NDA Number:	20-966
Approval Date:	March 30, 1999

Patent and Exclusivity Information:

U.S. Patent Number:	4,267,179
Expiration Date:	June 23, 2000
Type of Patent:	Drug Substance
Name of Patent Owner:	Janssen Pharmaceutica, N.V. Beerse, Belgium
Agent of Patent Owner:	Audley A. Ciamporcero One Johnson & Johnson Plaza New Brunswick, NJ 08933-7003

U.S. Patent Number:	4,727,064
Expiration Date:	February 23, 2005
Type of Patent:	Drug Product
Name of Patent Owner:	United States of America, represented by the Department of Health and Human Services

Patent and Exclusivity Information
SPORANOX® (itraconazole) Injection
Page 2

U.S. Patent Number:	4,791,111
Expiration Date:	December 23, 2005
Type of Patent:	Drug Substance Method of Use
Name of Patent Owner:	Janssen Pharmaceutica, N.V. Beerse, Belgium
Agent of Patent Owner:	Audley A. Ciamporcero One Johnson & Johnson Plaza New Brunswick, NJ 08933-7003

Exclusivity: Three years from the date of approval as provided by the Drug Price Competition and Patent Term Restoration Act of 1984

The undersigned declares that Patents 4,727,064 and 4,791,111 cover the formulation, composition, and/or method of use of SPORANOX® (itraconazole) Injection. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Date: February 25, 2000

Mary A. Appollina
Attorney for Applicant
Registered Patent Attorney
Registration No. 34,087

SPORANOX® (itraconazole) Injection, NDA 20-966
Amendment to Patent Information

TIME SENSITIVE PATENT INFORMATION

Amendment to Patent Information (item #13) for NDA 20-966

Active Ingredient:	Itraconazole
Strength:	10 mg/mL
Trade Name:	SPORANOX®
Dosage Form:	Injection
Route of Administration:	Intravenous
Approval Date:	March 30, 1999

Please revise the Patent and Exclusivity Information provided in the captioned NDA with the following:

U.S. Patent Number:	4,727,064
Expiration Date:	February 23, 2005
Type of Patent:	Drug Product
Name of Patent Owner:	United States of America, represented by the Department of Health and Human Services

Exclusivity: Three years from the date of approval as provided by the Drug Price Competition and Patent Term Restoration Act of 1984

The undersigned declares that Patent 4,727,064 covers the formulation, composition, and/or method of use of SPORANOX® (itraconazole) Injection. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Date: July 20, 2000

Mary A. Appollina

Mary A. Appollina
Attorney for Applicant
Registered Patent Attorney
Registration No. 34,087

EXCLUSIVITY SUMMARY for NDA # 20-966 SUPPL # 004
Trade Name Sporanox Generic Name Itraconazole
Applicant Name Janssen HFD- 590
Approval Date March 1, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

      YES /___/ NO /_X__/

      If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates

or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-966 - IV

NDA # 20-083 - CAPSULE

NDA # 20-657 - ORAL SOLUTION

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? N/A

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # ITR-INT-62

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results

of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1__, Study # ITR-INT-62

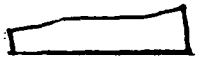
Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND  YES /__X_/ ! NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

/S/

Signature of Preparer — 8/20/01 Date

Title:

_____ _____

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- 590/Division File
HFD-590/RPM/Kimzey
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

EXCLUSIVITY SUMMARY for NDA # 20-657 SUPPL # 005
Trade Name Sporanox Generic Name Itraconazole
Applicant Name Janssen HFD-590
Approval Date March 1, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /__X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study N/A

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:_____

   d) Did the applicant request exclusivity?

      YES /___/ NO /_X__/

      If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /__X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety

(including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-966 - IV

NDA # 20-657 - ORAL SOLUTION

NDA # 20-083 - CAPSULE

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/
(BY REFERENCE)

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/NO /___/
(RELIED ON 20-966/004)

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # ITR-INT-62

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a <u>previously</u> approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/
(20966/004-SIMULTANEOUSLY APPROVED)
Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /__X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # ITR-INT-62
(RELIED ON FOR 20-966/004)

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted

or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND [redacted] YES /___/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

/S/ 7/20/01

Signature of Preparer Date
Title:

_____

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 020657
Trade Name: SPORANOX (ITRACONAZOLE) ORAL SOL 10MG/ML
Generic Name: ITRACONAZOLE
Supplement Number: 005 **Supplement Type**: SE1
Dosage Form:
Regulatory Action: AE **Action Date**: 3/1/01
COMIS Indication: ANTIFUNGALFOR THE TREATMENT OF ORAL OROPHARYNGEAL CANDIDIASIS

Indication #1: Empiric Therapy for Febrile Neutropenia
Label Adequacy: Does not apply
Formulation Needed: No new formulation is needed
Comments (if any)

Lower Range	Upper Range	Status	Date
0 years	Adult	Deferred	9/30/02
	Adult	Deferred	9/1/02

Comments: Unknown risk benefit ratio

This page was last edited on 7/27/01

Signature /S/ _____ Date 7/27/01

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 020966
Trade Name: SPORANOX (ITRACONAZOLE) 10MG/ML INJ
Generic Name: ITRACONAZOLE
Supplement Number: 004 **Supplement Type**: SE1
Dosage Form:
Regulatory Action: AP **Action Date**: 5/9/01
COMIS Indication: TREATMENT OF BLASTOMYCOSIS/HISTOPLASMOSIS AND ASPERGILLOSIS
IN IMMUNOCOMPROMISED AND NON-IMMUNOCOMPROMISED PATIENTS

Indication #1: Empiric Therapy of Febrile Neutropenia
Label Adequacy: Other - see comments
Formulation Needed: No new formulation is needed
Comments (if any) Deferred until September 30, 2002

Lower Range	Upper Range	Status	Date
0 years	Adult	Deferred	9/30/02

Comments: unknown risk benefit ratio

This page was last edited on 7/26/01

Signature 1S1 7103 Date 7/27/01

Debarment Certification

In accordance with the Generic Drug Enforcement Act of 1992, we certify that Janssen Research Foundation did not and will not use in any capacity the services of any person or firm debarred under subsections (a) or (b) [section 306(a) or (b) of the Federal Food, Drug and Cosmetic Act] in connection with NDA 20-966 for SPORANOX® (itraconazole) Injection.

We also certify that flawed Intel Pentium computer chips were not used to perform any analyses included in this supplement to NDA 20-966.

Janssen Research Foundation verifies that all trials conducted in the United States that are used to support this supplement to NDA 20-966 were conducted in compliance with the Institutional Review Board regulations in 21 CFR Part 56 and the informed consent regulations in 21 CFR Part 50. Non-US protocols used to support the claims in this application were reviewed by independent Ethics Committees/Review Boards and these trials were performed in accordance with the Declaration of Helsinki and its subsequent revisions.

Edward G. Brann
Assistant Director, Regulatory Affairs

Feb 24, 2000
Date

Debarment Certification

In accordance with the Generic Drug Enforcement Act of 1992, we certify that Janssen Research Foundation did not and will not use in any capacity the services of any person or firm debarred under subsections (a) or (b) [section 306(a) or (b) of the Federal Food, Drug and Cosmetic Act] in connection with NDA 20-657 for SPORANOX® (itraconazole) Oral Solution.

We also certify that flawed Intel Pentium computer chips were not used to perform any analyses included in this supplement to NDA 20-657.

Janssen Research Foundation verifies that all trials conducted in the United States that are used to support this supplement to NDA 20-657 were conducted in compliance with the Institutional Review Board regulations in 21 CFR Part 56 and the informed consent regulations in 21 CFR Part 50. Non-US protocols used to support the claims in this application were reviewed by independent Ethics Committees/Review Boards and these trials were performed in accordance with the Declaration of Helsinki and its subsequent revisions.

Edward G. Brann
Assistant Director, Regulatory Affairs

4-25-2000
Date

Date of Meeting:	December 11, 2000
Drug:	Sporanox (itraconazole)
Subject:	Congestive Heart Failure (CHF) in an itraconazole-treated population

Participants:

Janssen Research Foundation	Food and Drug Administration
Mark Klausner, M.D.	Shukal Bala, Ph.D.
Bruce Moskovitz, M.D.	Linda Gosey
Daniel Fife, M.D.	John Koerner, Ph.D.
Fred De Clerck, Ph.D.	Brad Leissa, M.D.
Karen De Beule, DHP	Regina Alivisatos, M.D.
Donna Ohye	Kathleen Uhl, M.D.
Edward Brann	Frank Cross
Graham Burton, M.D.	Imo Ibia, M.D.
Piet Dedoncker	Rosemary Johann-Liang
	Lisa M. Hubbard
	Hon-Sum Ko, M.D.
	Susan Walker, M.D.
	Robin Anderson, R.N., M.B.A.
	Robert DeLap, M.D.
	Owen McMaster, Ph.D.
	Sarah Singer, R.Ph.
	Mark Goldberger, M.D., M.P.H.
	Sandra L. Kweder, M.D.
	Rene Kimzey

Background: On September 8, 2000, a teleconference was held between Janssen and DSPIDP representatives to discuss labeling changes as proposed in labeling supplements NDA 20-657/S-004, 20-966/S-001 & 003, 20-083/S-025. During the teleconference, Edward G. Brann, Assistant Director of Regulatory Affairs for Janssen, discussed the finding of negative inotropic effects observed in an ongoing cardiovascular safety study with itraconazole. At this telecon, DSPIDP representatives requested additional information on this finding. Janssen submitted on October 26, 2000 a response to the inquiry along with an epidemiological study conducted by Herschel Jick, M.D., Boston University School of Medicine. This study evaluated the risk of developing congestive heart failure (CHF) in association with itraconazole use. The Agency requested a face-to-face meeting with Janssen to discuss cardiac risks associated with itraconazole use. These minutes record a summary of that meeting.

Meeting: Janssen representatives presented an overview of their findings related to CHF including pre-clinical cardiovascular effects, Studies ITR-BEL-98 and 104, and a summary of spontaneous report analysis of itraconazole and CHF from adverse event monitoring system. (See enclosed copy of overheads.)

The Office of Post-marketing Drug Risk Assessment (OPDRA) indicated that their analysis of adverse events was similar to the sponsors. However the sponsor identified increased risk of CHF with only calcium channel blockers, while OPDRA identified other cardiac drugs as well in the cases reviewed.

Dr. Goldberger asked whether the sponsor believed or not that itraconazole use is associated with a risk of CHF. The sponsor stated that they believe a risk does exist, but the magnitude of the risk for patients with a history of CHF is "very small" and for those with risk factors that it is "very, very small."

The Division of Dermatologic and Dental Drug Products (DDDDP) representatives (Drs. DeLap and Walker) indicated that, in their opinion, any significant risk of CHF associated with itraconazole use was unacceptable for patients being treated for uncomplicated onychomycosis.

Dr. Goldberger added that different risk/benefit profiles exist for the different indications. Both divisions encouraged the sponsor to vary their risk education program to fully address specific indications and insure it reached the appropriate specific clinical practitioner groups. Inherent in the educational program for drug risks and labeling must be an evaluation of its effectiveness in guiding clinicians.

The sponsor voiced agreement in concept to the implementation of an educational program and requested the Agency's advice in developing a new epidemiological study to assess cardiovascular risks.

Dr. Goldberger emphasized the Agency's interest in getting risk information to the public quickly.

From the perspective of a Risk Management Program, Dr. Leissa questioned whether the range of populations were diverse enough (e.g., ranging from aspergillosis to onychomycosis) to warrant the creation of a separate product label limited to the dermatologic indications.

The sponsor and the Agency agreed upon the following Action Items:

1. Design a non-clinical comparative study to assess antifungal, in vitro, cardiac risks.
2. Design a study with oral dosing in awake/instrumented animals to measure cardiac parameters
3. Sponsor to provide timelines to the Agency for items a through f below
    a. initial data availability
    b. completion of data analysis
    c. capsule study addressing dosing regimen
    d. draft epidemiological study to identify patients at risk for developing CHF
    e. educational program with measures of success
    f. Patient Package Insert (to be available very soon)
4. Sponsor to prepare and distribute "Dear Healthcare Provider" letter
    a. specific by indication
    b. to clinical generalist and specialist groups

Rene Kimzey, Project Manager
Division of Special Pathogen and
Immunologic Drug Products

Enclosure

Div. File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Date: June 21, 2000

From: Rene Kimzey, Project Manager
Phone (301) 827-2127
Fax (301) 827-2326

To: Edward G. Brann, Manager, Regulatory Affairs
Janssen Research Foundation
Phone (609) 730-3486
Fax (609) 730-3091

Subject: Janssen Record of FDA Contact for May 25, 2000
Sporanox (itraconazole)
NDA
Reference: [redacted] 20,657 and NDA 20-966

In your minutes of our telecon, in the paragraph titled, "Written Request", you state:

"Rosemary Roberts said FDA could issue a new WR covering both approved and unapproved indications where FDA knows there is a medical need for additional information. They would be clearly separated in the letter. The unapproved indication referred to is empiric therapy."

There appears to be some misunderstanding about what was said. The following comments attempt to clarify this discussion.

FDA cannot issue a single WR for both approved and unapproved indications. For the purposes of approved and unapproved indications, the Agency would need to issue two separate written requests; however, upon receipt of both WRs, the sponsor could choose which WR to follow. Hence, from a practical standpoint, the Agency will usually only issue a single WR for either approved or unapproved indications.

Based on the discussion between Janssen and CDER representatives at this telecon, the Agency agrees with Janssen that oropharyngeal candidiasis (OPC) is no longer a viable indication for the purposes of a WR. Furthermore, even though Sporanox Injection was recently approved for histoplasmosis, blastomycosis, and refractory aspergillosis, more pediatric populations will likely receive Sporanox for empirical therapy

Thus, the Agency proposes issuing a single WR for the active moiety (injection and oral solution) for ETFN. At this time, ETFN is not an approved indication for Sporanox. The Agency recommends the PPSR only address the active moiety (injection and oral solution) as it pertains to ETFN.

Please feel free to contact me at the above numbers for any questions or concerns.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: February 10, 2000

To: Edward G. Brann
Janssen Research Foundation
Phone (609) 730-3486
Fax (609) 730-3091

From: Rene Kimzey
Regulatory Project Manager
Phone (301) 827-2127
Fax (301) 827-2326

Subject: Itraconazole Empiric Therapy Trial ITR-INT-62

The following comments from the statistics reviewer are provided:

1. Please provide more detail on the randomization process. It is unclear exactly what procedure was used.
2. You state that "subjects who received 10 days of study medication and remained afebrile for 3 consecutive days" will be counted as a response. Please clarify whether this is only if such subjects do not satisfy any of the failure criteria.
3. Subjects with "bacterial or viral infection responsible for fever" will be counted as failures. Please summarize the number of patients with a bacterial infection responsible for fever by treatment group.
4. Your analysis of efficacy by prior use of antifungal prophylaxis suggests that the trial might have selected amphotericin B non-responders (efficacy rates are the same across treatment arms for those patients with no prior prophylaxis, however efficacy rates are substantially higher for itraconazole patients for those patients who did receive prior prophylaxis). Please summarize, by treatment group, (1) the number of patients who received amphotericin B as prior antifungal prophylaxis, and (2) the percent of these patients who did not respond to amphotericin B during the prior antifungal prophylaxis period.

5. Please examine efficacy in the subgroups of patients receiving antivirals versus those not receiving antivirals to determine if the co-administration of antivirals has an effect on outcome.
6. In your analysis of response and success rates, it is not clear how patients with no post-baseline data were treated (e.g., excluded or treated as failures). Please clarify how many such patients there are and how they are included in the analyses presented. In addition, it appears that you have not conducted the sensitivity analyses that you were planning for such patients (i.e., to count all as failures, to count itraconazole patients as failures and amphotericin B patients as successes, and to use estimated rates if the first two sensitivity analyses do not provide for a conclusion of equivalence). Please conduct these sensitivity analyses or justify why you have not (e.g., low numbers of such patients).
7. The per protocol analysis is only being done for the primary endpoint. Please perform this analysis for the various subgroups of interest also.
8. Unevaluable patients will be imputed as failures. Please perform sensitivity analyses to determine the effect of this imputation. Examples of such sensitivity analyses would include excluding these patients from the analysis and using their actual response (if available).

Please feel free to contact me at the above numbers for any questions or concerns.