CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-966**

PHARMACOLOGY REVIEW(S)

Reviewing Pharmacologist: Owen McMaster, PhD
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HFD-590

Sponsor: Janssen Research Foundation
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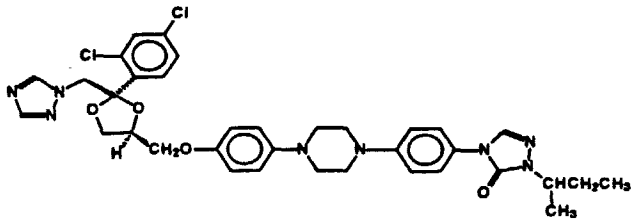
Drug: Sporanox (itraconazole) injection



Other name: R51-211
Chemical: Itraconazole, (±)-cis-4-(4-(4-(4-((2-(2,4-dichloro-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolon-4-yl)methoxy)phenyl)-1-piperazinyl)phenyl)phenyl)-2,4-dihydro-2-(1-methylpropyl)-3H1,2,4-trazol-3-one.
Molecular formula: $C_{35}H_{38}C_{12}N_8O_4$.
Molecular weight: 705.64

Formulation:

Related NDA'S: NDA 20-083, NDA 20-657

Indication: SPORANOX (itraconazole) intravenous is indicated for the treatment of histoplasmosis, blastomycosis and aspergillosis.

Introduction:

Itraconazole is a triazole antifungal closely related to a number of other antifungals such as ketoconazole (an imidazole). It is a potent inhibitor of fungal cytochrome P450-dependent synthesis of ergosterol, a vital component of fungal cell membranes. Its activity against a number of pathogenic fungal infections, including *Blastomyces dermatididis* and *Histoplasma capsulatum* led to the submission of an NDA 20-083 for its use in the treatment of blastomycosis and histoplasmosis. This NDA was withdrawn in April 1991 due to problems with formulation but resolution of the problem (reformulation) led to resubmission on Dec. 23, 1991. The NDA was approved in May 1992.

Itraconazole absorption can be irregular, and absorption is optimal if administered with a lipid containing meal and at an intra gastric pH. To bypass problems of poor absorption, itraconazole has been reformulated in a solution in hydroxypropyl-β-cyclodextrin. This increases absorption after an oral dose, and removes the lipid and pH dependency. Itraconazole oral solution, formulated in hydroxypropyl-β-cyclodextrin was approved in February, 1997.

This NDA has been submitted to support the approval of intravenous itraconazole.

Toxicology Studies Summary

The following studies were conducted with itraconazole intravenous formulated in Hydroxypropyl-β-cyclodextrin and were reviewed in this report unless otherwise indicated.

Acute Toxicity Studies

1 The acute intravenous toxicity of a clinical formulation containing itraconazole (10 mg/ml) and hydroxypropyl-beta-cyclodextrin (400 mg/ml) in mice. Janssen Research Foundation. December, 1989. Preclinical Research Report R051211/63.

2. The acute, intravenous toxicity of a clinical formulation containing itraconazole (10 mg/ml) and hydroxypropyl-beta-cyclodextrin (400 mg/ml) in rats. Janssen Research Foundation. December, 1989. Preclinical Research Report number R051211/62.

3. The acute toxicity of a clinical formulation containing 10 mg R051211 and 400 mg hydroxypropyl-beta-cyclodextrin per ml after intravenous infusion into dogs. Janssen Research Foundation, December 1989; Preclinical Research Report R051211/65.

4. One week Toxicity study in SPF Wistar rats. Department of Toxicology. Janssen Research Foundation, 2340 Beerse, Belgium. January 1992. Toxicological Research Report No. 2649.

5. One-month toxicity study in SPF Wistar rats. Janssen Research Foundation, June 1995; Toxicological Research Report No. 3437.

6. Three month tolerance study (DRF) in Wistar rats. Janssen Research Foundation, 2340 Beerse, Belgium. February 1996. Toxicological Research Report No. 3294.

7. One week toxicity study (DRF) in Beagle dogs. Janssen Research Foundation, 2340 Beerse, Belgium. June 1995. Toxicological Research Report No. 2650.

8. Two week pilot toxicity study in beagle dogs. Janssen Research Foundation, 2340 Beerse, Belgium. June 1995. Toxicological Research. Report No. 2141.

9. One month toxicity study in beagle dogs. Janssen Research Foundation, 2340 Beerse, Belgium. February 1996. Toxicological Research. Study No. 2139.

10. One month toxicity study in beagle dogs. Janssen Research Foundation, 2340 Beerse, Belgium. February 1996. Toxicological Research Report No. 3294

Other studies have been conducted with itraconazole and were reviewed in previous NDA 20-083 and NDA 20-657. Please refer to reviews of these NDA's for a discussion of the findings of these studies.

Special Toxicity Studies

11. Itraconazole. Immunotoxicity study in mice. Effect of a 28-day oral itraconazole treatment on the plaque forming cell response to the T cell-dependent antigen sheep red blood cells. Janssen Research Foundation, October 1993; Toxicological Research Report No. 2833.

12 Itraconazole. Immunotoxicity study in mice. Effect of a 28-day itraconazole treatment on the plaque forming cell response to the T cell-independent antigen DNP-Ficoll. Janssen Research Foundation, October 1993; Toxicological Research Report No. 2950.

13. The cytotoxicity of itraconazole (R051211) and hydroxypropyl-β-cyclodextrin (HP-β-CD, R081216) towards human and dog hepatocytes in primary cell culture. Janssen Research Foundation, August 1994; Nonclinical Pharmacokinetics Report R051211/R081216/FK 1731.

14. The acute oral toxicity of aged samples of itraconazole oral solution (10 mg/ml): a pilot study in female rats. Janssen Research Foundation, September 1994; Acute Toxicity

Report R051211. Non GLP.

Toxicology studies of Hydroxypropyl-β-cyclodextrin

1. The acute oral toxicity of R081216 in mice. Janssen Research Foundation, June 1989; Preclinical Research Report R081216/11.

2. The acute intravenous toxicity of hydroxypropyl-β-cyclodextrin (50%) in mice. Janssen Research Foundation, February 1988; Preclinical Research Report R081216/4.

3. The acute oral toxicity of R081216 in rats. Janssen Research Foundation, June 1989; Preclinical Research Report R081216/10.

4. The acute intravenous toxicity of hydroxypropyl-β-cyclodextrin (50%) in rats. Janssen Research Foundation, February 1988; Preclinical Research Report R081216/5.

5. The acute oral toxicity of R081216 in dogs. Janssen Research Foundation, June 1989; Preclinical Research Report R081216/9.

6. The acute toxicity of hydroxypropyl-β-cyclodextrin (20% w/v) after intravenous infusion into dogs. Janssen Research Foundation, November 1988; Preclinical Research Report R081216/7.

7. Hydroxypropyl-β-cyclodextrin. Twelve-month oral toxicity study in SPF Wistar rats. Janssen Research Foundation, July 1992; Toxicological Research Report No. 2163.

8. Hydroxypropyl-β-cyclodextrin. Subchronic toxicity study in Wistar rats (repeated dosage for 3 months followed by a 1-month recovery). Janssen Research Foundation, April 1989; Toxicological Research Report No. 2054.

9. Hydroxypropyl-β-cyclodextrin. Repeated dosage for 3 months followed by 1, 2 and 3-months recovery in rats. Janssen Research Foundation, January 1994; Toxicological Research Report No. 2693.

10. Hydroxypropyl-β-cyclodextrin. Twelve-month toxicity study in Beagle dogs. Janssen Research Foundation, July 1992; Toxicological Research Report No. 2164.

11. Hydroxypropyl-β-cyclodextrin. Subchronic toxicity study in Beagle dogs (repeated dosage for 3 months followed by a 1-month recovery). Janssen Research Foundation, March 1989; Toxicological Research Report No. 2055.

12. Hydroxypropyl-β-cyclodextrin. Subchronic toxicity study in Beagle dogs (repeated dosage for 3 months followed by 1, 2 and 3 months recovery). Janssen Research Foundation, March 1994; Toxicological Research Report No. 2694.

Carcinogenicity Studies

13. Hydroxypropyl-β-cyclodextrin. Three-month pilot toxicity study in SPF Swiss mice. Janssen Research Foundation, September 1993; Toxicological Research Report No. 2193. Non GLP.

14. Hydroxypropyl-β-cyclodextrin. Carcinogenicity study in Swiss mice. Janssen Research Foundation, November 1993; Toxicological Research Report No. 2166.

15. Hydroxypropyl-β-cyclodextrin. Carcinogenicity study SPF Wistar rats. Janssen Research Foundation, November 1993; Toxicological Research Report No. 2165.

Special Toxicity Studies

16. Hydroxypropyl-β-cyclodextrin. Three month + 1-month recovery toxicity study in SPF Swiss mice. Mechanistic toxicity study on liver changes. Janssen Research Foundation, February 1995; Toxicological Research Report No. 3040.

17. Hydroxypropyl-β-cyclodextrin. Two-week toxicity study in SPF Wistar rats. Mechanistic toxicity study on pancreas changes. Janssen Research Foundation, April 1994; Toxicological Research Report No. 2804.

18. Hydroxypropyl-β-cyclodextrin. Two-week toxicity study in SPF Wistar rats. Mechanistic toxicity study on pancreas changes. Janssen Research Foundation, June 1994; Toxicological Research Report No. 2857.

19. Hydroxypropyl-β-cyclodextrin. Four-day pilot toxicity study in SPF Wistar rats. Janssen Research Foundation, November 1992; Toxicological Research Report No. 2621. Non GLP.

20. Hydroxypropyl-β-cyclodextrin. Ten-day pilot toxicity study in SPF Wistar rats. Janssen Research Foundation, June 1993; Toxicological Research Report No. 2795. Non GLP.

21. Hydroxypropyl-β-cyclodextrin. Repeated dose toxicity study in SPF Wistar rats (3 months). Janssen Research Foundation, January 1995; Toxicological Research Report No. 3283.Non GLP.

22. Hydroxypropyl-β-cyclodextrin. Four-day pilot toxicity study in Beagle dogs. Janssen Research Foundation, November 1992; Toxicological Research Report No. 2652. Non GLP.

23. Primary irritation study in rabbits single dose.Janssen Research Foundation, June 1989; Toxicological Research Report No. 2158.

24. Hydroxypropyl-β-cyclodextrin. Primary eye irritation study in Albino rabbits. Janssen Research Foundation, March 1995; Toxicological Research Report No. 1633.

25. Hydroxypropyl-β-cyclodextrin. Primary eye irritation study in Albino rabbits. Janssen Research Foundation, March 1995; Toxicological Research Report No. 1634.

26. Beta-cyclodextrins as vehicles in eye-drop formulations an evaluation of their effects on rabbit corneal epithelium. Lens and Eye Toxicity Research 1990:7(3&4):459-68.

Reproduction Studies

27. Hydroxypropyl-β-cyclodextrin. Male and female fertility study in Wistar rats (Segment I). Janssen Research Foundation, April 1993; Toxicological Research Report No. 2161.

28. Hydroxypropyl-β-cyclodextrin. Male and female study in Wistar rats (Segment I). Janssen Research Foundation, May 1990; Toxicological Research Report No. 2157.

29. Hydroxypropyl-β-cyclodextrin. Embryotoxicity and teratogenicity study in Sprague-Dawley rats (Segment II). Laboratoires Janssen Aubervilliers, July 1989; Toxicological Research Report No. 2186.

30. Hydroxypropyl-β-cyclodextrin. Embryotoxicity and teratogenicity study in Wistar rats (Segment II). Janssen Research Foundation, March 1990; Toxicological Research Report No. 2155.

31. Hydroxypropyl-β-cyclodextrin. Embryotoxicity and teratogenicity study in New Zealand white rabbits (Segment II). Laboratoires Janssen Aubervilliers, July 1989; Toxicological Research Report No. 2160.

32. Hydroxypropyl-β-cyclodextrin. Embryotoxicity and teratogenicity study in Albino rabbits (Segment II). Janssen Research Foundation, January 1993; Toxicological Research Report No. 2515.

33. Hydroxypropyl-β-cyclodextrin. Embryotoxicity and teratogenicity study in New

rabbits (Segment II). Janssen Research Foundation, May 1990; Toxicological Research Report No. 2156.

34. Hydroxypropyl-β-cyclodextrin. Peri- and postnatal reproduction study in Wistar rats (Segment III). Janssen Research Foundation, January 1993; Toxicological Research Report No. 2748.

35. Hydroxypropyl-β-cyclodextrin. Intravenous peri- and postnatal study in Wistar rats (Segment III). Janssen Research Foundation, August 1990; Toxicological Research Report No. 2162.

36. Hydroxypropyl-β-cyclodextrin. Peri- and postnatal reproduction study with a second generation evaluation in Wistar rats (Segment III). Janssen Research Foundation, June 1993; Toxicological Research Report No. 2865.

37. Hydroxypropyl-β-cyclodextrin. *Salmonella typhimurium* gene reverse mutation test (Ames test). Janssen Research Foundation, July 1989; Toxicological Research Report No. 2202.

38. Hydroxypropyl-β-cyclodextrin. *Escherichia coli*. Reverse mutation assay. Janssen Research Foundation, November 1994; Toxicological Research Report No. 3382.

39. Evaluation of the mutagenic activity of beta-hydroxypropylcyclodextrine in an in vitro mammalian cell gene mutation test with L5178Y mouse lymphoma cells (with independent repeat). RCC Notox B.V. Toxicological Research Report No. 951, August 1991.

40. Evaluation of DNA repair inducing ability of β-hydroxypropyl cyclo-dextrin in a primary culture of rat hepatocytes (with independent repeat). RCC Notox, August 1991; Toxicological Research Report No. 949.

41. Hydroxypropyl-β-cyclodextrin. Chromosome aberration in cultured human peripheral lymphocytes.Janssen Research Foundation, June 1991; ToxicologicalResearch Report No. 2462.

42. Hydroxypropyl-β-cyclodextrin. Micronucleus test in mice. Janssen Research Foundation, January 1991; Toxicological Research Report No. 2238.

43. Hydroxypropyl-β-cyclodextrin. Micronucleus test in mice. Janssen Research

Foundation, May 1990; Toxicological Research Report No. 2237.

Toxicology Studies Review

1. The acute intravenous toxicity of a clinical formulation containing itraconazole (10 mg/ml) and hydroxypropyl-beta-cyclodextrin (400 mg/ml) in mice. Janssen Research Foundation, December 1989; Preclinical Research Report R051211/63. Study # 8948

Five male and five female adult Swiss mice per group were administered a formulation of itraconazole (10 mg/mL, Batch BEA111) and hydroxypropyl-ß-cyclodextrin (400 mg/mL) in water at pH 4.0. The compound was administered intravenously at a dose of 44.1 mg/kg itraconazole and 1764 mg/kg of hydroxypropyl-ß-cyclodextrin. A second group of five animals per sex were administered placebo which contained the same formulation with the exception of itraconazole (the active drug). The animals were observed for 14 days and their body weights recorded at days 0, 4, 7, 10 and 14. At the end of the study (14 days), the animals were necropsied and examined for gross abnormalities of organs and tissues.

No mortalities were recorded. A drug related hyperventilation was seen in two of the males and three of the females immediately after dosing. By one hour, the breathing had returned to normal.

2. The acute intravenous toxicity of a clinical formulation containing itraconazole (10 mg/ml) and hydroxypropyl-beta-cyclodextrin (400 mg/ml) in rats. Janssen Research Foundation, December 1989; Preclinical Research Report R051211/62. Study # 8947.

Five male and five female adult Wistar rats per group were administered a formulation of itraconazole (10 mg/mL, Batch BEA111) and hydroxypropyl-ß-cyclodextrin (400 mg/mL) in water at pH 4.0. The compound was administered intravenously at a dose of 17.6 mg/kg itraconazole and 704 mg/kg of hydroxypropyl-ß-cyclodextrin. A second group of five animals per sex were administered placebo, which contained the same formulation with the exception of itraconazole (the active drug). The animals were observed for 14 days and their body weights recorded at days 0, 4, 7, 10 and 14. At the end of the study (14 days), the animals were necropsied and examined for gross abnormalities of organs and tissues.

No mortalities were recorded. A drug related hyperventilation was seen in three of the males and four of the females immediately after dosing and exophthalmos in one of the females. By one hour, the breathing had returned to normal.

. The acute toxicity of a clinical formulation containing 10 mg R051211 and 400 mg hydroxypropyl-beta-cyclodextrin per ml after intravenous infusion into dogs. Janssen Research Foundation, December 1989; Preclinical Research Report R051211/65.Study # 8946.

One male and one female adult beagle dog per group were administered a formulation of itraconazole (10 mg/mL, Batch BEA111) and hydroxypropyl-ß-cyclodextrin (400 mg/mL) in water at pH 4.0. The compound was administered intravenously at a dose of 17.6 mg/kg itraconazole and 704 mg/kg of hydroxypropyl-ß-cyclodextrin. A second group of five animals per sex were administered placebo which contained the same formulation with the exception of itraconazole (the active drug). The animals were observed for 14 days and their body weights recorded at days 0, 4, 7, 10 and 14. At the end of the study (14 days), the animals were necropsied and examined for gross abnormalities of organs and tissues.

No mortalities were recorded. One female had dyspnea and the loss of the righting reflex immediately after infusion. Animals in both the treated and placebo group exhibited licking of the infusion site after dosing.

4. One week Toxicity study in SPF Wistar rats. Department of Toxicology. Janssen Research Foundation, 2340 Beerse, Belgium. January 1992. Toxicological Research Report No. 2649.

SPF Wistar rats, 5 weeks old, 5 rats /sex/dose group, were treated with intravenous itraconazole (10 mg/kg), once daily, for one week. Control rats were untreated or treated with the excipient hydroxypropyl-beta-cyclodextrin.

No animals died during this study. Treatment of rats with intravenous itraconazole at 10 mg/kg produced a slight reduction in body weight gain (25 % less than controls) and food consumption (12 % less than controls) in females. Segmented neutrophils were reduced by 66%, lymphocytes were increased by 13% and BUN was increased by 41 % in males only. Increased cholesterol (+93 % in females, + 14 % in males) phospholipids (52% in females only), relative adrenal weights (+ 13% in males and + 26 % in females) were also associated with the administration of intravenous itraconazole. Three of the five females treated with 10 mg/kg itraconazole showed swollen uterus with watery content.

Intravenous itraconazole was tolerated in rats at 10 mg/kg/day for one week. Toxic effects included increased cholesterol and phospholipids increased adrenal weights as well as swollen uterus (with watery content).

5.One-month toxicity study in SPF Wistar rats. Janssen Research Foundation, June 1995. Toxicological Research Report No. 3437.

6. Three month tolerance study (DRF) in Wistar rats. Janssen Research Foundation, 2340 Beerse, Belgium. April 1995. Toxicological Research Report No. 3294. Drug batch number ZR051211PUB451. HPBCD batch number 094A05-560.

This study was designed to determine the toxic effects of intravenously administered itraconazole in combination with hydroxypropyl-beta-cyclodextrin (1:40 ratio), when administered at 0, 5 and 10 mg/kg/day. Drug was infused over one hour at 0.15 or 0.3 ml/100g/hour. Records were kept of mortality and clinical observations (daily), body weights and food consumption (weekly), hematology, serum analysis and urinalysis after one month and terminally. Post mortem studies included organ weights, gross pathology and histopathology.

After three months of dosing, itraconazole produced a 15 % increase in WBC's in males only at 10 mg/kg. This change was also seen in the vehicle control group and was therefore seen as a vehicle-related finding. Neutrophil count changes were erratic (increased in males (+60 %) and decreased in females (-44 %) at one month and unchanged in males and increased in females at 3 months. At the end of 3 months monocyte counts were increased (+150 %) in the 10 mg/kg males and in vehicle controls. Cholesterol (+ 49 %, males, +12 % females), triglycerides (-62 % males, -68 % females), BUN (+ 27 % males, +21 % females) and creatinine (+21 % males) were affected by the high dose of itraconazole. These changes were also seen in the vehicle-treated animals except for the changes in cholesterol, which seemed to be drug-related. Changes in phospholipids were inconsistent and/or slight. AST (2.8 times control in males and 1.4 times control in females in the high dose) and ALT (3.2 times control in males and 1.5 times control in females in the high dose) were increased in the high dose after three months, with vehicle controls also showing increases. Decreased urinary pH (low and high dose animals), urinary volume (vehicle, low and high dose males and low dose females) and occult blood (all drug and vehicle treated groups) were also associated with itraconazole treatment. Relative lung, kidney and adrenal weights were increased in vehicle and drug treated animals with increases of + 32 and + 115 % in the lungs, +40 and +33 % in the kidneys and +52 and +46 % in the adrenals in males and females respectively at the high dose. After three months, swollen adrenals were observed in low and high dose females. This finding was associated with swollen cortical cells. Pale kidneys were seen in both males and females treated with vehicle or itraconazole. Kidney findings were associated with vacuolation of cortical and medullary tubuli and swelling of pelvic epithelial cells. Kidney changes seem to be related to the administration of HPBCD. Several vehicle and drug treated animals showed swollen centrilobular hepatocytes. Changes in the lung after three months included intra-alveolar foamy macrophages and a focal thickening of alveolar septae which were seen in all groups except controls. These were therefore likely to be related to the vehicle. Swollen epithelial cells of the urinary bladder were observed in both vehicle and itraconazole treated animals and so may be related to the vehicle.

Conclusion

Changes associated with administration of intravenous itraconazole included effects in the kidney, lungs, adrenals and liver. Cholesterol, triglyceride and BUN changes were also observed.

7. One week toxicity study in beagle dogs. Janssen Research Foundation, Beerse, Belgium. Study number 2650. Report N84310. March 1989.

This study was designed to determine the tolerability of 10 mg/kg itraconazole when given to beagle dogs once daily for one week.

Two groups of dogs, two/sex/dose group, were treated with either vehicle (hydroxypropyl-beta cyclodextrin, 400 mg/kg) or itraconazole (10 mg/kg, formulated in hydroxypropyl-beta cyclodextrin). Records were kept of mortality, clinical observations, body weight, hematology, serum analysis and urinalysis.

No animals died. Dogs treated with 10 mg/kg itraconazole showed increased white blood cells (+ 30 %), reduced cholesterol (-24 %), reduced triglycerides (-34 %) and reduced phospholipids (-23 %).

One week of treatment with intravenous itraconazole, formulated in HPBCD, was well tolerated by beagle dogs.

8. Two-week pilot toxicity study in beagle dogs. Janssen Research Foundation, Beerse, Belgium. Study 2142. Report N71078. February, 1989.

This study was designed to determine the maximum dose of itraconazole that would be tolerated in dogs treated for two weeks. This information was used to select the dose used in the one-month study.

Groups of beagle dogs, one dog/sex/dose group, were treated by intravenous bolus with a number of experimental compounds including itraconazole, 10 mg/kg, formulated in HPBCD and HPBCD (500 or 1000 mg/kg). Records were kept of mortality, clinical observations, heart rate and EKG, body weights, hematology, serum analysis and urinalysis. Organ weights and gross pathology were also recorded.

The only significant change observed was an increase in ALT to approximately three times the control levels, indicating an effect in the liver of these animals.

In conclusion, intravenous itraconazole, 10 mg/kg, was well tolerated in beagle dogs

treated for two weeks.

9. One-month toxicity study in beagle dogs. Janssen Research Foundation, 2340 Beerse, Belgium. October 1989. Toxicological Research Study 2139.

[redacted]

10. One-month toxicity study in beagle dogs. Janssen Research Foundation, 2340 Beerse, Belgium. February 1996. Toxicological Research Report No. 3294

Groups of beagle dogs, 4 dogs/sex/dose group were treated intravenously with vehicle (hydroxypropyl-beta-cyclodextrin) or 5, 7.5 or 10 mg/kg itraconazole once daily. The tretment was unfused over 30 minutes. There was also a group of untreated control animals.

Animals treated with itraconazole at doses below 10 mg/kg/day for one month showed few side effects but those treated at 10 mg/kg experienced sedation, decubitus, pale mucosa and cyanosis.

Cardiac changes were slight: PQ interval was reduced slightly (-9%) and systolic blood pressure decreased by 10 % at 10 mg/kg after one month. Systolic pressure was also however lower in drug-treated animals predose.

Dogs dosed at 10 mg/kg for one month showed a 13 % decrease in body weight compared to controls. Food consumption was 33 % (week 3) and 23 % (week 4) less than controls. These animals also showed an 11 % decrease in hematocrit, 9 % decrease in red blood cell count. Basophils were decreaased by approximately 50 % at all doses and thrombocytes were reduced by between 10 and 40 % at all doses in weeks 2 and 4. Decreases in calcium (-8 %) total protein (-15 %), albumin (-12 to -18 % weeks 2 and 4) and cholesterol (-25 % weeks 2 and 4) were seen in animals treated at 10 mg/kg for one month. Phospholipids (reduced by 15 to -30 %) at 7.5 and 10 mg/kg, total bilirubin (+ 50 and + 183 % increased at 2 and 4 weeks at 10 mg/kg), alkaline phosphatase (+ 32, + 207% increased at 2 and 4 weeks at 10 mg/kg), AST (1.6 and 1.9 times control at 2 and 4 weeks at 10 mg/kg) and ALT (1.8 to 4.2 times control at 7.5 and 10 mg/kg at 2 and 4 weeks) were also affectd by itraconazole treatment.

Thymus weights were reduced by about 40 % at all doses while adrenals weights increased by 29, 49 and 89 % at low mid and high doses. Lung weights increased by 13, 20 and 66 % at low mid and high doses. There was a slightly increased incidence of foci in the lungs at all dose levels. Swollen cortical cells were noted in the adrenal glands at all dose levels. There was also an increase in thymic involution at all dose levels, and in the liver, an increase in dark eosinophilic hepatocytes at 7.5 and 10 mg/kg. Swollen vacuolated cells of the reticulo endothelial system and Kuppfer cellsand the presence of foamy macrophages in

lymphoid tissues and the lung were also observed. Vacuolated renal cortical tubuli and swollen epithelial cells in the urothelium, were thought to be related to the vehicle administration, but urinary parameters were unaffected.

Treatment of beagle dogs with intravenous itraconazole for one month (30 minute infusion) produced toxic effects at all doses. Prominent changes were seen in the kidney, adrenals, liver and lungs.

Toxicity Studies: Focus on hydroxypropyl beta-cyclodextrin.

In single dose toxicity studies of HP-β-CD, transient episodes of soft defecation or diarrhea were noted in mice, rats, and dogs. Vomiting and licking were observed in dogs as well. HP-β-CD, given for twelve months (rats were given HP-β-CD through the diet and dogs were dosed by gavage) produced dose-dependent urinary tract changes consisting of vacuolated epithelial cells in urinary bladder and renal pelvis in rats and dogs. Vacuolated renal tubuli were found in rats only. At high doses (2000 and 5000 mg/kg bwt) in rats, toxicity was mainly characterized by a lower body weight, slight hematological changes, and several serum chemistry changes (e.g. increases in chloride, aspartate aminotransferase, and alanine aminotransferase). Urinalysis revealed increases in creatinine, specific gravity, white blood cells, urobilinogen, calcium oxalate crystals, proteins, and granular casts and decreases in urinary pH and volume in males. The urine of females contained bacteria, and at 5000 mg/kg bwt also granular casts and occult blood. At autopsy, an increased weight of the pancreas and, only at 5000 mg/kg bwt, increased weights of the kidneys, adrenals (females) and lungs (males) were present. The kidneys were found to have a pale appearance. Histopathological changes were seen in the liver (centrilobular swelling, prominent Kupffer cells and hepatocytic vacuolation) and, at 5000 mg/kg, in the lungs (foamy cells). The hepatotoxic effects (increased liver transaminases and altered histology) at high doses of HP-β-CD (2000 and 5000 mg/kg) are either completely (transaminases) or almost completely (histological changes) reversible within a 1-month recovery period. In dogs, repeated oral administration of HP-β-CD at 2000 mg/kg resulted in the occurrence of soft stools.

HP-β-CD did not cause ocular irritation or irritation at a parenteral injection site. Findings from two short-lasting (4 days) infusion studies in rats and dogs demonstrate that urinary tract changes, resembling those after oral and intravenous (bolus injection) dosing, are also present after intravenous infusion. Thus, the occurrence of these histological adaptive alterations is not influenced by the mode of administration.

The reproductive function of male and female rats, dosed orally up to 5000 mg/kg, and intravenously up to 400 mg/kg, with HP-β-CD, was not adversely affected. Paternal and maternal toxicity were mainly characterized by a slightly decreased body weight gain. No primary embryotoxic effect was evidenced in rats or rabbits. Associated with maternal toxicity, decreased survival, and reduced birth weight and body weight evolution of the pups

were noted in rats at oral doses of 2000 and 5000 mg/kg and at an intravenous dose of 400 mg/kg. In a second, undosed generation, all variables were normal. In rabbits, dosing at an oral, maternally toxic dose of 1000 mg/kg resulted in a slight embryotoxic effect, evidenced by increased skeletal variations. No adverse effects were noted after an intravenous dose of up to 400 mg/kg . No clearly teratogenic effects were noted in any study. No mutagenic potential was evidenced in any of the studies performed to investigate the potential of HPβCD to induce DNA-damage, point and/or gene mutations, and chromosome aberrations in *in vivo* and in vitro test systems.

Carcinogenic potential of HP-β-CD

When HP-β-CD was given in the diet (to mice for 22-23 months and to rats for 25 months, at doses of 0, 500, 2000, and 5000 mg/kg), in rats, the main finding was an increase in exocrine pancreas neoplasia at 500, 2000 and 5000 mg/kg. A slight increase in neoplasms in the large intestine at 5000 mg/kg was also seen but may be part of an adaptive hypertrophy of the large intestines after high doses of polysaccharides and other osmotically active nutrients. In mice, a trend for a slight increase in hepatocytic neoplasm was seen in males.

Table 5: Incidence of non-neoplastic and neoplastic changes in the pancreas

Male rats	0 mg/kg	500 mg/kg	2000 mg/kg	5000 mg/kg	p [d]
non-neoplastic changes					
focal hyperplasia	39	42	45	43	
neoplastic changes					
exocrine neoplasia	23/49	37/50[b]	35/50 [a]	37/48[b]	0.0030
- adenoma	22/49	37/50[b]	35/50 [a]	37/48[b]	0.0016
- adenocarcinoma	2/49	4/50	9/50 [a]	7/48[a]	0.0227
Female rats	**0 mg/kg**	**500 mg/kg**	**2000 mg/kg**	**5000 mg/kg**	**p [d]**
non-neoplastic changes					
focal hyperplasia	19	26	33[a]	42[c]	
neoplastic changes					
exocrine neoplasia	4/49	8/50	16/50[b]	22/49[c]	0.0000
- adenoma	4/49	7/50	15/50[b]	20/49[c]	0.0000
- adenocarcinoma	0/49	1/50	2/50	4/49	0.0243

Chi-square (one-tailed): [a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$

[d] One-sided p-value for trend. Test for positive trend, Peto monograph, WHO, IARC, Lyon 1980, pp.311-426, dose levels 0,1,2,3.

Table 6: Incidence of non-neoplastic and neoplastic changes in the large intestine

Male rats	0 mg/kg	500 mg/kg	2000 mg/kg	5000 mg/kg	p [d]
non-neoplastic changes					
cecum hypertrophy	3/49	10/49	36/49[c]	41/48[c]	
colon hypertrophy	1/49	0/50	20/48[c]	40/49[c]	
rectum hypertrophy	0/49	0/50	19/50[c]	40/49[c]	
neoplastic changes					
adenocarcinoma	0/50	0/50	1/50	4/50	0.0050
Female rats	**0 mg/kg**	**500 mg/kg**	**2000 mg/kg**	**5000 mg/kg**	**p [d]**
non-neoplastic changes					
cecum hypertrophy	0/50	0/49	16/50[c]	45/49[c]	
colon hypertrophy	0/50	0/49	4/50	41/49[c]	
		0/49	1/50	38/49[c]	
neoplastic changes					
- adenocarcinoma	0/50	0/50	050	1/50	0.2569
- adenoma	0/50	0/50	0/50	1/50	0.2830

Chi-square (one-tailed): [a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$ [d]One-sided p-value for trend. Test for positive trend, Peto monograph, WHO, IARC, Lyon 1980, pp.311-426.

Conclusion:

Hydroxypropyl-ß-cyclodextrin in the feed of rats clearly caused acinar pancreatic neoplasms in both male and female rats. The label of the drug has been edited to reflect the presence of the pancreatic neoplasms.

Overall Conclusion

Itraconazole, formulated in hydroxypropyl-beta-cyclodextrin, and injected intravenously repeatedly is associated with changes in the liver, kidney, adrenals, thymus, urinary tract, and lungs. Sufficient information has been provided to support this NDA. There are no preclinical Pharmacology or Toxicology issues that would preclude the approval of this NDA. The information included in the label reflects that needed for the proper use of this

drug product in the clinic.

/S/

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Concurrences:
HFD-590/KHastings 3/27/99
HFD-590/RAlbrecht

Disk:
HFD-590/KHastings
cc:
HFD-590
HFD-590 Division File
HFD-590/Micro/LGosey
HFD-340
HFD-590/MO/
HFD-590/CSO/
HFD-590/Pharm/OMcMaster
HFD-590/Chem/
HFD-345