CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

20-657/S-004, S-005

MICROBIOLOGY REVIEW

Microbiology Review

Division of Special Pathogen and Immunologic Drug Products

(HFD-590)

NDA# 20-966

Reviewer : Linda Gosey
Correspondence Date : 9-22-00
CDER Receipt Date : 9-22-00
Review Assigned Date: 9-26-00
Review Complete Date: 2-09-01

Sponsor: Janssen Pharmaceuticals
1125 Trenton-Harbourton Rd
PO Box 200
Titusville, New Jersey 08560

Submission Reviewed: Efficacy Supplement-S004

Drug Category: Antifungal

Indication: Empiric therapy in febrile neutropenic patients with suspected fungal infections

Dosage Form: Intravenous Injection 200 mg/vial and 10 mg/mL solution

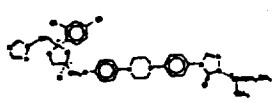
Product Names:

a. Proprietary: Sporanox®

b. Nonproprietary: Itraconazole, R051211

c. Chemical: (+)-1-[(RS)-sec-butyl]-4-[p[[2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl-Δ-1,2,4-triazolin-5-one

Structural Formula:



Supporting Documents: [redacted]

Background:

The sponsor, Janssen, submitted 2 supplemental new drug applications 20-966 (S-004) and 20-657 (S-005) for the use of the intravenous and oral solution formulations of itraconazole in the empiric therapy of suspected fungal infections in febrile neutropenic patients. The proposed dose for this new indication is 200 mg IV BID (2 one-hour infusions) for 2 days, followed by 200 mg IV QD (one one-hour infusion) for 3 – 7 days. Itraconazole IV can be continued up to a total of 14 days. Treatment should be continued with SPORANOX® Oral Solution 200 mg (20 mL) BID until resolution of the clinically significant neutropenia or 28 days.

Itraconazole is indicated for the treatment of Blastomycosis, pulmonary and extrapulmonary; Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal Histoplasmosis; and Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy. The oral solution is also approved for the treatment of oropharyngeal Candidiasis.

Febrile neutropenic patients are at an increased risk for developing invasive fungal infections (IFIs). For patients with hematological malignancies the incidence of IFIs at autopsy is 20-50%. Risk factors for fungal infections in neutropenic patients include, long term exposure of broad-spectrum antibiotics, steroid use, treatment with chemotherapeutic agents, indwelling catheters and environmental exposure. Colonization of yeast in the gastrointestinal tract or oral cavity may also increase the risk for developing IFIs. Lastly, patients who receive a bone marrow transplant (BMT) and develop chronic graft-versus-host disease also appear to be at risk for developing IFIs.

For the majority of febrile neutropenic patients the demonstration of the causative pathogen producing the fever is not possible prior to initiating antifungal therapy. This is due to the fact that there is a high rate of mortality with IFIs and the window of time to initiate antifungal therapy is short. In clinical practice, febrile neutropenic patients who do not respond to antibiotic therapy after 3-5 days are started on empiric antifungal therapy. When conducting a phase III clinical trial it is generally preferable to have documented proof that the antifungal agent is active against a causative fungal pathogen. However, in this clinical trial defervescence while on antifungal therapy was used as a surrogate marker for efficacy.

Yeasts and moulds both can produce IFIs in patients with hematological malignancies. *Candida albicans* is the most common fungal pathogen followed by *Aspergillus fumigatus*, *C. glabrata*, *C. tropicalis*, *C. krusei* and *A. flavus*. New and emerging fungal pathogens include *Cryptococcus neoformans*, *Trichosporon beigelii*, *Rhizopus* and *Penicillium marneffei*. While the activity profile of an antifungal agent is critical in the overall clinical outcome of a neutropenic patient

with a presumed fungal infection, it is important to remember that the immune status of the subject also has a major impact on the patient's response.

Summary:

In this submission the sponsor did not include any new pre-clinical microbiology data. Therefore, there will be no pre-clinical microbiology review.

This efficacy supplement is for a new clinical indication. For the new indication the sponsor conducted a single phase III clinical trial to assess the safety and efficacy of IV and oral itraconazole in the empiric therapy of febrile neutropenic subjects with hematologic malignancies. The microbiology review of the clinical data is discussed below.

Clinical Trial Synopsis:

The efficacy data were derived from a single clinical trial, ITR-INT-62. This was a multi-center, open-label, comparative, randomized clinical trial of itraconazole versus amphotericin B in febrile neutropenic patients with hematologic malignancies who had presumed fungal infections. Subjects enrolled in this study came from 30 centers in Europe, Canada, Australia, and the US. A total of 384 patients were enrolled, 192 per study arm.

Subjects had to meet the following inclusion criteria:

- an underlying hematologic malignancy undergoing chemotherapy or BMT (excluding allogenic BMT)
- a baseline ANC of < 500 cells/mm^3 for at least 7 days
- fever of > 38° C not responding to 3–7 days of appropriate antimicrobial therapy.

Subjects were excluded for the following reasons:

- proven or suspected deep fungal infection (including all cases without mycological sampling) diagnosed during previous episodes of neutropenia, and still present
- liver disease defined as liver enzymes (SGPT or SGOT) > 5 times the upper normal limit or bilirubin > 50 mol/liter at trial entry
- proven deep fungal infection at trial entry defined as either a positive culture from a normally sterile site (except for urine), a positive histopathology from any site or a highly suggestive CT-scan
- proven systemic bacterial or viral infection at trial entry or a superficial bacterial or viral infection responsible for the fever

Subjects were withdrawn from the clinical trial if:

- a serious adverse event occurred
- the investigator considered it, for safety reasons, in the best interest of the subject that he/she be withdrawn
- the subject withdrew his/her consent
- an exclusion criterion was met during the trial
- lack of efficacy
- a proven infection with a fungal species not considered susceptible to itraconazole was documented (*Fusarium* spp., *Mucor* spp.)

Patients received study medication until the end of neutropenia, defined as one day where the neutrophil count is higher than 0.5×10^9/L or 2 days with a neutrophil count $> 1.0 \times 10^9$/L, however, therapy was not to exceed 28 days. The first 4 doses of IV itraconazole were administered at 200 mg BID followed by 5 days of 200 mg QD itraconazole. If required by the clinical condition of the subject, itraconazole at 200 mg QD could be continued for another week. Oral itraconazole, 200 mg, was then administered without a meal BID from day 8 or day 15 onwards. Amphotericin B was administered such that a total daily dose of ≥ 0.7 mg/kg had to be obtained within the first 48 hours. An amphotericin B dose of ≤ 1 mg/kg had to be maintained throughout the entire study period. When minor side effects occurred the daily administration of amphotericin B was lowered to 0.5 mg/kg without withdrawing the subject for intolerance. All liposomal formulations of amphotericin B were not allowed in this study.

At randomization, a complete clinical evaluation of all subjects was made including a chest X-ray 24 hours prior to randomization. If pulmonary abnormalities were present a bronchoscopy was performed prior to study entry. Throughout the study the patient's clinical signs were monitored. Information collected included body temperature (three times a day), white blood cell count, neutrophil count and signs and symptoms possibly attributable to fungal infection. Bronchoalveolar lavage (BAL) and biopsies were performed if indicated. Clinical specimens were collected for fungal, bacterial and, if needed, viral cultures from blood, urine and other suspected sites. All results, including routine fungal surveillance cultures obtained since initiation of fever were reported. Clinical data were collected daily during treatment up to the end of neutropenia. Evaluations were also made on all subjects who discontinued prematurely or failed.

The following criteria were required for a patient to be defined as a therapeutic cure:

- patient survival with resolution of fever and neutropenia within 28 days of treatment
- absence of emergent fungal infections
- no discontinuation of therapy due to toxicity or lack of efficacy with treatment for three or more days.

Failures could be due to either a lack of efficacy (i.e. continued fever while on therapy) or due to toxicity concerns (i.e. inability to tolerate the drug).

Efficacy failures were defined as:

- documented deep fungal infection
- clinical and microbiologic documented bacterial or viral infection responsible for fever
- death after >3 days of study medication
- persistent fever at the end of neutropenia or at day 28
- deterioration of signs and symptoms potentially attributable to deep fungal infection whether the fever had disappeared or not at the end of neutropenia or at day 28
- fever requiring a change in empirical antifungal therapy

Failure due to poor tolerance of study medication was the only criteria for classifying patients as a safety/toxicity failure.

Clinical trial ITR-INT-62 was designed such that defervescence, sustained survival, and documented fungal infection could be individually assessed as efficacy parameters. Because patients with presumed fungal infections were enrolled in this trial the documentation of fungal infections was not required. As a consequence, fever, the need to change antifungal therapy due to non-response, deterioration of clinical signs and symptoms and survival were surrogate markers for efficacy failures for this clinical trial.

In the intent-to-treat analysis the sponsor determined a success rate of 47% in the itraconazole group and 38% in the amphotericin B group. While the sponsor's success rates appear to be similar between the two arms the data that were of interest with respect to microbiology dealt with the failures. As a result this microbiology review will focus on patients who were classified as failures. Table 1 shows the number of subjects in each arm that were in the various analyses. The microbiology assessment focused on the final intent-to-treat (ITT) patient population.

Table 1
Patient Populations Evaluated

Subjects Evaluated	ITR	AM B	Total
Total Recruited	197	197	394
1^0 Safety Analysis	192	192	384
Final ITT	179	181	360

ITR= Itraconazole; AMB=Ampohtericin B

The ITT patients were then classified according to their clinical response during the study. In the itraconazole and amphotericin B arms there were 24/179 (13%) and 44/181 (24%) subjects,

respectively, that received less than 3 days of study medication and were thus categorized as non-evaluable. There was a total of 84/179 (47%) and 69/181 (37%) subjects in the itraconazole and amphotericin B patients, respectively, that met the criteria for cure (See table 2). This table corresponds to table 13 from the medical officer's review.

Table 2
Response Rate
ITT Population

Response	Itraconazole		Amphotericin B	
	N = 179	100%	N = 181	100%
Cure Total	84	47%	68	37%
Cure (not unevaluable or failure)	52	29%	44	25%
Cure (10 days medication and afebrile)	32	18%	24	13%
Unevaluable (R/x < 3 days)	24	13%	44	24%
Failure Total	71	40%	69	37%
Failure (documented clinical or microbiological infection)	7	4%	8	5%
Failure (Insufficient response)	6	3%	5	3%
Failure (Persistent fever at end of neutropenia)	20	11%	10	6%
Failure (change in antifungal/x due to fever)	17	10%	1	1%
Failure (Documented deep fungal infection or CT)	5	3%	5	3%
Failure (Intolerance)	12	7%	38	21%
Failure (Deterioration of signs and symptoms)	2	1%	0	-
Failure (Death after > 3 days)	2	1%	2	1%

As previously discussed neutropenic patients with presumed fungal infections were enrolled in the study. In the ITT population cure rates of 84/179 (47%) and 68/181 (37%) were seen in the itraconazole and amphotericin B arms, respectively. There were 71/179 (40%) and 69/181 (38%) failures in the itraconazole and amphotericin B arms, respectively. In this study there were 8 possible definitions for a failure. To further assess the efficacy, or lack there of, failures were divided into efficacy failures (patients remaining febrile, having documented fungal infection or patients requiring a change in antifungal therapy) or failures due to intolerance. Because documented infections were not necessary in this clinical trial, responses defined as deterioration of signs and symptoms, requiring a change in antifungal therapy, persistent fever at the end of

neutropenia and documented clinical or microbiologic infection were used as surrogate markers for determining presumed fungal infections or therapeutic failures. Thus failures could be more broadly classified as failures because the patient was unevaluable, failure due to a presumed or documented fungal infection or failure due to drug intolerance as seen in table 3.

Table 3
Patient Responses Categorized by Efficacy or Intolerance

Response	ITR N=179	AM B N=182
Cure	84(47%)	69(38%)
Failure because Unevaluable	24(13%)	44(24%)
Failure due to Intolerance	12(7%)	38(21%)
Failure due to Lack of Efficacy	59(33%)	31(17%)

ITR=Itraconazole; AMB=Amphotericin B

The data from table 3 show that there were 3 times as many failures due to intolerance in the amphotericin B arm versus the itraconazole arm. This was to be expected, as amphotericin B is quite toxic. However, when failure due to lack of efficacy was assessed it was noted that twice as many patients failed to respond in the itraconazole arm versus the amphotericin B arm. These data suggest that febrile neutropenic patients with presumed fungal infections are twice as likely to respond if amphotericin B is administered, assuming they can tolerate the drug. Again, this is not surprising, as amphotericin B is a cidal drug versus itraconazole, which is a static antifungal agent.

In most clinical trials clinical signs and symptoms are the primary endpoints; with microbiologic results as secondary endpoints confirming the etiologic agent(s) producing the clinical signs and symptoms. In this clinical trial fever was a surrogate marker for a presumed fungal infection as it was difficult to obtain clinical samples to document invasive fungal infections. There were only 5 documented cases of fungal infections in each of the itraconazole and amphotericin B treatment arms. In the itraconazole arm the documented fungal infections were 1 *Aspergillus fumigatus* from the BAL, 1 *C. guillermondii* from the blood, 1 *C. krusei* from the blood, 1 *Aspergillus sedowi* from the blood and BAL, and 1 patient with *Candida* species, *Aspergillus* species and *Geotrichum* species from a BAL. In the amphotericin B arm there were 3 patients with *Aspergillus fumigatus*, 1 patient with *C. glabrata* isolated from a BAL and 1 *C. albicans* recovered from the blood. The non-albicans strains of *Candida* and *Aspergillus* strains producing

the documented fungal infections suggests that both amphotericin B and itraconazole are less active against these pathogenic fungi versus *C. albicans* isolates.

In this clinical trial the sponsor did not determine the in vitro susceptibility testing of the isolates against itraconazole or amphotericin B. Therefore, it is unknown whether or not the isolates of the various fungal species from the 10 documented cases of fungal infections are susceptible or resistant to either itraconazole or amphotericin B.

After review of the microbiologic results from the rest of the ITT patients that failed it is impossible to determine the cause for the lack of efficacy in many subjects. This is due to the fact that the microbiology data set that was submitted in this SNDA is confusing or incomplete. What can be noted is that many of the patients that were in the "Failure due to lack of efficacy" category did have fungi that were recovered either from the stool, rectum, throat or BAL. Fungal colonization of the gastrointestinal tract and oral cavity is a known risk factor for developing systemic fungal infections in febrile neutropenic patients with hematological malignancies. Therefore, without additional microbiologic data these subjects cannot be ruled out as having a potential invasive fungal infection. At best the clinical data demonstrate that failure due to lack of efficacy is twice as likely to occur in subjects who take itraconazole versus amphotericin B. It is this reviewer's opinion that these findings should be placed in the clinical trials section of the product label.

Labeling:

The microbiology section of the product label will not be changed. Therefore, with respect to microbiology the microbiology section of the label is acceptable.

Conclusions:

In this submission the sponsor is seeking approval of intravenous and oral itraconazole for empiric therapy of presumed fungal infections in febrile neutropenic patients with hematological malignancies. The active arm in this study was amphotericin B. Neutropenic patients are susceptible to viral, bacterial and fungal infections. One of the earliest signs of an infection in this patient population is fever. Neutropenic patients that become febrile are generally started on antibiotic therapy. If fever persists 3-5 days after antibiotic treatment is started then empiric antifungal therapy is initiated. Delaying the initiation of antifungal therapy until the fungal pathogen can be isolated is not recommended as the risk of death increases over time.

It is well known that febrile neutropenic patients can become infected with *Candida* and *Aspergillus* species. Amphotericin B, including the liposomal preparations, has been the standard of care for empiric antifungal therapy, although free amphotericin B is not specifically approved for empiric therapy. Amphotericin B is a cidal agent, which has good activity against *Aspergillus*

species and *Candida* species. Itraconazole is an azole antifungal agent that exhibits static activity. Itraconazole is approved for first line treatment of Histoplasmosis and Blastomycosis and as second-line therapy for the treatment of Aspergillosis.

In clinical trial ITR-INT-62 the primary parameter of efficacy was "response at the end of therapy (EOT)" defined as the absence of failure or unevaluability. Efficacy parameters included defervescence, survival, the elimination of clinical signs and symptoms associated with presumptive fungal infection and the presence or absence of documented fungal infections. Patients were discontinued if toxicity was demonstrated, they failed therapy or they received less than 3 days of treatment. In the ITT population the cure rates were comparable in both treatment arms, 47% and 37% in the itraconazole and amphotericin B arms, respectively. From a microbiologic perspective the various reasons for failure were of interest and further investigated.

In the design of this clinical trial there were 8 definitions for failure. To simplify the analysis failures were separated into 3 basic categories, failure because the patient was unevaluable, failure due to intolerance to the medication and failure due to lack of efficacy. In the itraconazole and amphotericin B arms there were 13% and 24% unevaluable patients, respectively. When failure due to intolerance was assessed it was noted that there were three times as many failures in the amphotericin B arm versus the itraconazole arm. This was to be expected as amphotericin B is toxic and treatment related adverse events are common. When failure due to lack of efficacy was determined there were 59 (33%) and 31 (17%) failures in the itraconazole and amphotericin B treatment arms, respectively. The higher failure rate due to the lack of efficacy observed in patients receiving itraconazole suggests that itraconazole is not as effective as amphotericin B in resolving fever in neutropenic subjects with presumed fungal infections. Because defervescence was a surrogate marker for efficacy and microbiologic evidence of confirmed fungal infection was not available on the majority of the patients that did not resolve their fever it can only be presumed that the lack of efficacy seen in these subjects could be due to a potential fungal infection. The microbiologic data from the five patients in each treatment arm that did have a documented invasive fungal infection show that in both treatment arms the infections were due to non-albicans species of *Candida*, *A. fumigatus*, and other *Aspergillus* species.

In conclusion, with respect to microbiology itraconazole should be approved for empiric therapy in febrile neutropenic patients with suspected fungal infections pending the sponsor's agreement to accurately describe the higher failure rates due to lack of efficacy in the clinical trials section of the product label.

Recommendation:

With respect to microbiology this itraconazole efficacy supplement should be approved pending the sponsor's agreement to accurately describe the higher failure rates due to lack of efficacy in the clinical trials section of the product label.

/S/

Linda L. Gosey
Microbiologist (HFD 590)

Concurrences:

HFD-590/Dep Dir _ /S/ Signature 2/22/01 Date
HFD-590/Micro TL _____ Signature 2/16/01 Date

CC:

HFD-590/Orig.NDA#20-966
HFD-590/Division File
HFD-590/MO:Alivasatos
HFD-590/CSO:Kimzey
HFD-590/Chem:
HFD-590/Pharm:Mc Master
HFD-590/Review Micro:Gosey