DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 27 1997

TRANSMITTED VIA FACSIMILE

Cynthia Chianese
Janssen Pharmaceutica Inc.
Janssen At Washington Crossing
1125 Trenton-Harbourton Rd.
Post Office Box 200
Titusville, New Jersey 08560-0200

RE: NDA # 20-083
Sporanox (itraconazole capsules)
MACMIS ID #4244

Dear Ms. Chianese:

This letter concerns Janssen Pharmaceutica Inc.'s (JPI) promotional materials for the marketing of Sporanox (itraconazole capsules). Based on promotional materials and other information the Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed as part of its surveillance and monitoring program, we have concluded that JPI is disseminating false and/or misleading promotional materials for Sporanox.

Promotion of an Unapproved Dosing Regimen

It is our understanding that JPI has disseminated to health care providers promotional labeling that contains claims that state or suggest that Sporanox is safe and effective when used in the treatment of onychomycosis of the toenail with a pulse dosing regimen of 200 mg b.i.d. for 1-week per month for 2-4 months. The currently approved dosing regimen for the treatment of onychomycoses of the toenail is 200 mg once daily for 12 consecutive weeks. Sporanox has been approved for pulse dosing in onychomycosis of the fingernail; however, such approval has not been granted for onychomycosis of the toenails.

DDMAC has reason to believe that JPI's promotional materials promote Sporanox for use in this pulse dosing regimen for onychomycosis of the toenails has included, but are not limited to:

- a copy of a journal reprint entitled "Pulse Therapy with One-Week Itraconazole Monthly for Three or Four Months in the Treatment of

Onychomycosis," (CUTIS; 56, September, 1996). This article reports the results of an open study of the pulse dosing regimen in 28 patients with onychomycosis of the toenails. Further, a handwritten note is alleged to have accompanied this reprint that suggests that this study supports the use of the pulse dosing regimen in the treatment of onychomycosis of the toenails. (See attached)

- A calendar (JPI-SP-089) with handwritten instructions for the pulse dosing regimen for the treatment of onychomycosis of the toenails. (See attached)

Promotion of Comparative Claims

JPI's labeling pieces also include misleading claims of safety (i.e., no requirement for monitoring of liver function tests) and comparative efficacy (i.e., superior cure rates compared to other approved drugs for onychomycosis, and suggestions of efficacy for unapproved uses) for Sporanox that are inconsistent with Sporanox's approved labeling.

For example, DDMAC has obtained the following Sporanox promotional materials that were alleged to have been disseminated by Janssen representatives in various locations throughout the United States:

- a chart comparing Sporanox to Lamisil. This chart states that liver monitoring is required with Lamisil but not with Sporanox when used in the pulse dosing regimen for onychomycosis of the toenails. However, Sporanox's approved labeling carries a WARNING related to the potential for hepatitis, and the subsequent requirement for liver function monitoring.

  The chart also makes unsubstantiated comparative efficacy claims for Sporanox over Lamisil. Specifically, the chart claims that Sporanox's efficacy rates exceed those of Lamisil without support from adequate and well-controlled comparative trials; up to 93% and up to 80% for Sporanox and Lamisil, respectively. (See attached)

- a letter to a Pharmacy and Therapeutics Committee petitioning for unrestricted status for Sporanox. The letter claims that Sporanox is highly efficacious with cure rates of 70-84%. However, the letter fails to provide that for patients with onychomycosis, the mycological cure rate was 54%, the overall success rate (combined mycological cure and clinical cure) was only 35%, with a mean time to overall success of approximately 10 months, as provided in Sporanox's approved labeling. The letter also suggests that

Sporanox is safe and effective when using a pulse dosing regimen for the treatment of onychomycosis of the toenails. Finally, the letter makes unsubstantiated claims of superior efficacy for Sporanox over griseofulvin. (See attached)

Promotion of Unapproved Uses

DDMAC has also obtained promotional materials that state or suggest that Sporanox is safe and effective for the treatment of superficial dermal infections, tinea corporis, tinea cruris, and tinea pedis using the pulse dosing regimen. Sporanox is not currently indicated for the treatment of these superficial dermal infections.

Other

DDMAC has obtained a copy of a newsletter article that was distributed to patients of two medical centers. The newsletter article recommends Sporanox's use in the pulse dosing regimen for the treatment of onychomycosis of the toenails.

The article also states that Sporanox is fungicidal. This claim is inconsistent with Sporanox's labeling that states that Sporanox is fungistatic. Further, the article fails to present any balancing information about the risks, warnings or precautions associated with Sporanox's use.

Finally, this newsletter states that it was supported by an "Educational Grant from Janssen." However, a footnote to the article states that this information was "Submitted by Janssen," thereby implying that JPI may have exerted editorial influence over the content of the newsletter.

Failure to File

Most of the materials that are the subject of this letter were not submitted to FDA by JPI pursuant to the post-marketing reporting requirements for promotional labeling and advertising, 21 CFR §314.81(b)(3).

JPI should respond in writing by April 11, 1997, describing the actions it has taken and those it will take to discontinue the dissemination of these materials.

DDMAC recommends that JPI's actions include informing its sales representatives that promotion of Sporanox for unapproved dosing regimens, or unsubstantiated comparisons to other anti-fungal products, is in violation of the Federal Food, Drug,

and Cosmetic Act, and could result in further regulatory action. In addition, sales representatives should be advised that dissemination of "homemade" pieces that have not been submitted to FDA pursuant to the post marketing reporting requirements is a violation of the law.

If JPI had any questions or comments, please contact Mr. Jean E. Raymond, PA, by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Room 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

In all future correspondence related to this matter, please refer to MACMIS ID #4244, in addition to the NDA number.

Sincerely yours,

Jean E. Raymond, P.A.

Jean Raymond, PA
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

Attachments

Pulse Therapy with One-Week Itraconazole Monthly for Three or Four Months in the Treatment of Onychomycosis

Piet De Doncker, MSc, PhD, Wilrijk, Belgium
J. Van Lint, MD, Arendonk, Belgium
P. Dockx, MD, PhD, Wilrijk, Belgium
D. Roseeuw, MD, PhD, Brussels, Belgium

In an open study, twenty-eight patients with toenail onychomycosis were treated with monthly cycles of 400 mg itraconazole daily for one week for three (n=5) or four (n=23) consecutive months. In this patient sample, a total of seventy-one toenails were affected, with a mean nail-plate involvement of 55 percent (range, 20 to 100 percent). *Trichophyton rubrum* was the most frequently isolated pathogen, followed by *T. mentagrophytes*. After active therapy, patients were evaluated for a maximum period of two years (mean, twelve months). A total of twenty-six of twenty-eight patients (93 percent) were considered as clinically cured. Of the remaining two patients, one was markedly improved and one appeared to have relapsed. Only three of seventy-one nails still exhibited some pathologic involvement. Of the twenty-six patients considered cured, mycologic examination at the final visit was performed on thirteen and the results were negative in all of them. The remaining clinically cured patients had no mycologic examination at the last visit. This short treatment was well tolerated; the only adverse reaction being a mild headache in one patient. Patients preferred this regimen to receiving daily treatment for three months.

Pulse therapy consisting of monthly one-week cycles of 400 mg itraconazole daily for three to four months may offer a new option for treatment of onychomycosis. Further large-scale studies are required to confirm these findings.

From the Departments of Dermatology, University of Antwerp, Wilrijk, Belgium, and Free University of Brussels, Brussels, Belgium.
REPRINT REQUESTS to the Department of Dermatology, U.Z. Antwerpen, Wilrijkstraat 10, 2650 Edegem, Belgium (Dr. De Doncker).

In the past the treatment of onychomycosis has posed a serious problem to the clinician because of this condition's recalcitrance to therapy and the dystrophic changes in the affected nails.[1] In contrast to some other diseases, spontaneous cures hardly ever occur and the disorder runs an extremely prolonged course. Therefore, treatment of onychomycosis has been hampered by the long treatment course as well as the lengthy duration of the healing process, the occurrence of side effects, poor responses, and a high rate of recurrences.[2]

The advent of new and more effective antifungal therapies constitutes a turning point in the treatment of cutaneous fungal infections, especially onychomycosis.[3-5] Drug therapy is no longer restricted to long-term treatment, which has traditionally been associated with low cure and high relapse rates. Pharmacokinetic studies of these new drugs have clearly shown the importance of different penetration routes to the skin and nails. Our thinking on the treatment of superficial infections has consequently changed, so that short and fixed treatment regimens have been devised.[6-10] At present, the standard treatment regimen with itraconazole and terbinafine consists of daily dosing for six and twelve weeks for fingernail and toenail infections, respectively.[6]

The concept of continuous treatment for onychomycosis, even when administered for a maximum of three months, seems to have been surpassed by the recent tendency to administer an intermittent or pulse-dose regimen with one week of itraconazole therapy per month.[8-10] Early results with the pulse-dose regimen encouraged us to continue and to evaluate the acceptance of this approach in a second study in patients with onychomycosis.

Patients and Method

Patients—Twenty-eight patients (eleven male and seventeen female) entered this open study. Outpatients with a clinical diagnosis of toenail onychomycosis confirmed by results of mycologic examination were eligible for the study. Women of childbearing age were asked to use ade-

TABLE I

PATIENT CHARACTERISTICS

Gender	
Mean age (yrs) +/- SD	
Mean duration (yrs) +/- SD	
Mean percentage affected area at start +/- SD	
Culture Results	
T. rubrum	
T. mentagrophytes	
T. mentagrophytes + *T. rubrum*	
T. mentagrophytes + *Scopulariopsis brevicaulis*	
Scopulariopsis brevicaulis	
Candida albicans	
Nondermatophyte spp.	
Negative	
Not available	

quate contraceptive methods. Patients were excluded if they were under 18 or over 75 years of age, pregnant or lactating, had advanced liver disease, or were concomitantly using rifampicin, phenytoin, cyclosporin A, anticoagulant agents, or antacid treatment. Oral and topical antifungal therapies were stopped three months and two weeks before the start of the study, respectively.

Treatment

Patients were instructed to take 200 mg itraconazole twice a day for seven consecutive days during the first week of each month for three or four months. After these monthly cycles of one week, patients were evaluated for a maximum of two years.

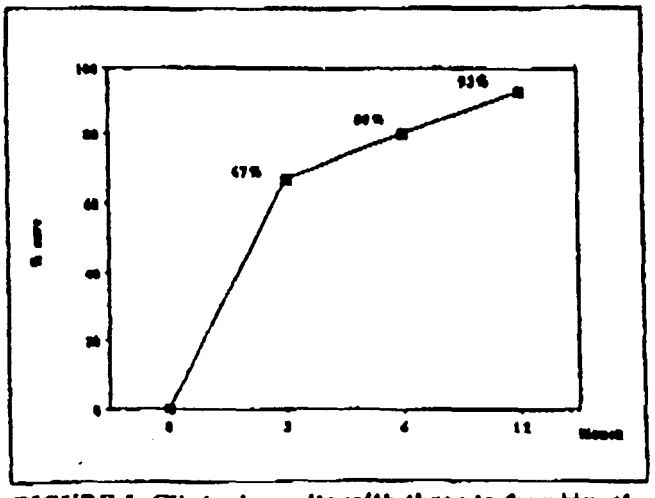

FIGURE 1. Clinical results with three to four monthly cycles of one-week 400 mg itraconazole in patients with toenail onychomycosis.

Assessment

Patients were evaluated clinically at baseline and at regular intervals up to twelve months. The area of the affected nails was estimated as the percentage of the nail exhibiting pathologic change. Mycologic examination was done by direct microscopic evaluation and culture. Mycologic cure was defined as results of negative potassium hydroxide examination and negative findings on culture.

Patients who were cured or whose condition was markedly improved were defined as responders to treatment.

At the start of treatment, patients were asked directly which treatment approach they preferred: pulse or short-term continuous therapy for three months. If they clearly preferred pulse treatment, the feasibility of this regimen was checked: if they could accept an intermittent regimen or if they were likely to forget a cycle was assessed.

All spontaneously reported adverse events were recorded.

Results

The demographic data and the mycologic results from twenty-eight patients at baseline are shown in Table I. *Trichophyton rubrum* was the most frequently isolated organism at the start, followed by *T. mentagrophytes*. A total of seventy-one toenails were infected, with an average pathologic fraction of the nail plate of 55 percent. All but five patients received four monthly one-week cycles of 400 mg itraconazole daily. Those five patients received three of these cycles.

At month three, 67 percent of the patients already showed a clinical response (Figure 1). This response rate had increased to 80 percent by month six and to 93 percent by the final visit (average, twelve months). At this visit, twenty-six of the twenty-eight patients were considered clinically cured. Of the remaining patients, one was markedly improved and one had relapsed.

Of the twenty-six patients considered cured, mycologic studies at the final visit were performed on thirteen. The results of these tests showed a 100 percent mycologic cure. The remaining thirteen clinically cured patients had no mycologic examination at the last visit. Two patients had a toenail onychomycosis caused by *Scopulariopsis brevicaulis* and responded very well to the 400 mg dose.

All patients in this study sample choose the one-week pulse regimen over the three-month continuous dosing. The preference was more pronounced in patients who had already experienced continuous treatment. The pulses were well tolerated; the only adverse reaction being a mild headache in one patient.

Case Report

A 34-year-old female patient had onychomycosis of the big toenail (Figure 2A) for twenty-four months. Investigations revealed a potassium hydroxy-positive nail and a positive culture for *Trichophyton rubrum*. A positive culture for *Scopulariopsis brevicaulis* was isolated at month two.

The patient received four monthly cycles of one-week 400 mg itraconazole daily. After two treatment cycles significant improvement was observed (Figure 2B), with further improvement at month four and month 6 (Figure 2C). The patient was cured at the twelve-month follow-up visit (Figure 2D).

Comments

The present study confirms that pulse therapy in patients with onychomycosis is effective and that it may be a superior approach for the treatment of this chronic disease. In the first pilot study including fifty patients, this regimen resulted in cure rates ranging from 65 to 75 percent and response rates of 88 percent (three pulses) and 84 percent (four pulses).[8] Similar results with an equal tolerability profile were obtained in this study. Other oral antifungal agents such as ketoconazole, fluconazole, and terbinafine are also being studied with different pulse-dose regimens, which have shown variable success rates.[9-11] Based on their kinetic profile in the nail and plasma, each drug will have its own characteristics and therefore be most efficacious in a specific adapted pulse treatment.

The advantages of pulse dosing seem obvious. First, the schedule is easy to adapt. It can be tailored to the clinical situation and the individual patient; for example, the number of pulses can be modified to the severity of nail involvement or to possible interaction with drugs or to concomitant diseases, such as diabetes, vascular peripheral insufficiency, and others. This also enables the physician to evaluate outcome more closely and to intervene when necessary. Flexible therapy for nail infections is also preferred more and more, since there is still some concern about safety during long-term systemic treatment. Pulse therapy also seems to improve patient compliance.[9,11] In this way notorious one-year treatments of onychomycosis with griseofulvin or ketoconazole would become a thing of the past.[8]

Another consideration is that at a time when health economics is becoming increasingly important, pulse treatment with itraconazole has led to a substantial saving.

Lastly, pulse therapy is highly suited to being combined with topical antifungal therapy. However, the combination approach still needs to be investigated in a number of studies.

In conclusion, the use of the pulse regimen with itraconazole may open up a novel perspective in the treatment of nail infections.

REFERENCES

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9. Rosseuw D, De Doncker P: New approaches to the treatment of onychomycosis. *J Am Acad Dermatol* 29(1): S45-S50, 1992.
10. Rosen T: New approaches to the diagnosis and management of onychomycosis. *Int J Dermatol* 33: 289-299, 1994.
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16. Faergemann J, Zehender H, Jones T, et al: Terbinafine levels in serum, stratum corneum, dermis-epidermis (without stratum corneum), hair, sebum and eccrine sweat. *Acta Derm Venereol* 71: 322-326, 1990.
17. Finlay AY, Lever LR, Thomas R, et al: Nail matrix kinetics of oral terbinafine in onychomycosis and normal nails. *J Dermatol Treat* 1 (Suppl) 2: 51-54, 1990.
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Sporanox 100mg

1. 93% Cure Rate — Onychomyc
2. NO LFT's necessary

DERMATOPHYTE or RINGWORM INFECTIONS

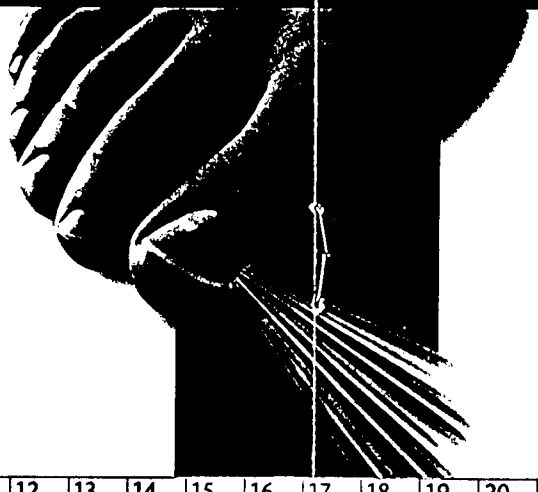
ONYCHOMYCOSIS:	**200 mg. bid X 7 days. Off for 3 weeks**	
	FINGERNAILS	**3 months of therapy**
	TOENAILS	**4 months of therapy**
TINEA CORPORIS:	**200 mg. qd X 7 days**	
TINEA CRURIS:	**200 mg. qd X 7 days**	
TINEA PEDIS:	**200 mg. qd X 14 days**	
TINEA MANUUM:	**200 mg. qd X 14 days**	
TINEA CAPITIS:	**200 mg. qd X 14 days**	

AM + daily = toe

CANDIDA INFECTIONS:

VAGINAL CANDIDIASIS:	**200 mg. qd X 3 days**	
	or	**200 mg. bid X 1 day**
ORAL THRUSH:	**100 mg. qd X 15 days**	
CUTANEOUS CANDIDIASIS:	**200 mg. qd X 7 days**	

200 mg BID 1 week a mon
for 3-4 months.



REMEMBER TO TAKE SPORANOX AS DIRECTED

Each time you take SPORANOX, mark an X in the box for that day

QUESTIONS? CALL 1-800-595-NAILS (1-800-595-6245)

100 mg
sporanox®
(itraconazole capsules)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

SPORANOX VS. LAMISIL

"THE TRUE STORY ON SAFETY"

	SPORANOX	LAMISIL
ADVERSE REACTIONS	Headache 1% GI Upset 4% Rash 3% Liver Elevations 4% *Not seen with Sporanox	Headache 13% GI Upset 16% Rash 5% Liver Elevations 3% *Taste Disturbance 3% (May Last Up To 5 wks after Discontinuation of Therapy) Visual Disturbance
LIVER MONITORING	NO (Not Required w/ Pulse Dose)	YES
USE IN RENAL IMPAIRED PATIENT	YES	NO
HEMATOLOGIC ABNORMALITIES	NO	YES (Neutropenia, Leucopenia, Lymphopenia, Pancytopenia)
BLOOD MONITORING (CBC)	NO	YES (Patients Using Lamisil who are known or suspected of having Immunodeficiency)
PERSISTENCE IN PLASMA POST THERAPY (JOURNAL AMER. ACAD. DERM 1993)	1-2 wks	4-8 wks
DRUG INTERACTIONS	Seldane, Hismanal, Propulsid Oral Triazolam, Cyclosporine, nticoagulants, Oral lycemics	Tagamet, Rifampin *No Studies have been conducted on interactions with the following drugs. Oral Hypoglycemics, Hormones, Theophylline, Thiazides, Phenytoins, Beta Blockers and Calcium Channel Blockers.

It has come to my attention that you and many of your colleagues who treat onychomycosis with Sporanox (itraconazole) would like to have Sporanox available on drug formulary as an "unrestricted" agent rather than requiring "prior authorization". To meet this end, at the request of many, I have put together a letter, with supporting references, that petitions the pharmacy and therapeutics committee for this change. You are welcome to reproduce this letter on your letterhead and make any modifications that you deem appropriate. If you have any further suggestions or comments, please do not hesitate to contact me. Thank your for your support.

Sincerely,

/

ENCLOSURE

RE: Change in formulary status of Sporanox (itraconazole).

Dear Chairman,

It is my recommendation that the formulary status of the oral antifungal pharmaceutical, Sporanox, be changed from "prior authorized" to "unrestricted" for the treatment of onychomycosis. Onychomycosis is a disease that has a significant medical, social, and economic impact. Sporanox, superior to any other currently available antifungal, has proven to be highly efficacious, safe, and cost-effective treatment for onychomycosis.

The impact of onychomycosis may be well under-appreciated. It is estimated by the Center for Disease Control that 11 million Americans suffer from onychomycosis. A recent pilot survey conducted at Massachusetts General Hospital revealed that of patients who responded, 35% reported pain, 25% mild dysthesia, and 15% loss of fine touch. Twenty-percent, 20% had difficulty with small object retrieval, 15% claimed to avoid participating in their favorite hobbies because of embarrassment or impaired performance, and 10% reported that the condition interfered with their job. In addition, 40% said that onychomycosis interfered with social relationships and 25% that it interfered with professional relationships. An unpublished, industry-sponsored survey of Medicare patients in the U.S. indicated that fungal nail infections accounted for 1,300,000 physician visits during a 1-year period. The patients paid an average of two visits to their physician, the total cost of which exceeded $43 million.[1]

Sporanox is highly efficacious, with demonstrated cure rates (70% to 84% clinical)[2] that far exceed that of the currently unrestricted agent, griseofulvin (15% to 40% clinical)[3] in

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[1] Elewski B, and Hay R. International Summit on Cutaneous Antifungal Therapy. Journal of the American Academy of Dermatology 1995; 33:816-22.

[2] De Doncker P, et al. Antifungal pulse therapy for onychomycosis: A pharmacokinetic and pharmacodynamic investigation of monthly cycles of 1 week pulse therapy with itraconazole. Archives of Dermatology 1996; 132-134.

the treatment of onychomycosis. Sporanox offers dramatically lower relapse rates relative to griseofulvin (10% to 20% versus 70% to 90%, respectively)[4]. In addition, the duration of Sporanox therapy is significantly shorter; a pulse dosing of one week per month for three months as compared to12 to 18 months of continuous dosing with griseofulvin.

Sporanox exhibits a favorable safety profile and is well tolerated by patients. While Sporanox is contraindicated for concomitant use with terfenadine, astemizole, cisapride, and triazolam, the most commonly reported adverse events in U.S. clinical trials were elevated liver enzymes (4%), gastrointestinal disorders (4%), and rash (3%)[5].

Sporanox is cost-effective treatment for onychomycosis. For example, in treating a typical toenail infection, the prescription cost of Sporanox (pulse-dosed at 200 mg BID, 1 week/month for 3 months) therapy for onychomycosis ranges, locally, between $480 and $540. Depending upon the patient's weight and the duration of therapy, the prescription cost of griseofulvin ranges, locally, between $585 and $1,170.

All facts considered regarding necessity, efficacy, safety, and cost-effectiveness, Sporanox is an obviously superior pharmaceutical agent for the treatment of onychomycosis. Therefore, I strongly petition that the formulary status of Sporanox be revised from "prior authorized" to "unrestricted".

Sincerely,

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[3] Hay R.J. Onychomycosis: agents of choice. Dermatol Clin 1993;11:161-169.

[4] Rousseau D, and De Doncker P. New approaches to the treatment of onychomycosis. Journal of the American Academy of Dermatology 1993;29(suppl):S45-S50.

[5] Janssen Pharmaceutica, Inc. Sporanox (itraconazole) package insert revised April 1995.

Janssen Pharmaceutica Inc.
NDA# 20-083

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Drafted:	Raymond	Date: 11/1/96
Revised:	Fleischer	Date: 11/21/96
Comment:	Baylor-Henry	Date: 12/9/96
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Revised:	Fleischer	Date: 12/23/96
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Revised:	Raymond	Date: 2/20/97
Concur :	Palmer	Date: 3/26/97

MACMIS ID# 4244

CC:
HFD-40/(20-510)(20-083)
HFD-40/Chron/(Raymond)/(Palmer)
HFD-540/(Wilkin/Labib/KozmaFornaro)
HFD-540/NDA# 20-083/20-510

MACMIS Type Code: Lett.
MACMIS Action Code: viol
2253 ID#:
Material ID#:
Due Date:
Close Out: N

FOI STATUS: Releaseable