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Itraconazole (Sporanox[®]) for Vulvovaginal Candidiasis

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ABSTRACT

Vulvovaginal candidiasis is a common occurrence among women over 25 years of age. The likelihood of developing infection increases with pregnancy, the use of oral contraceptives or antibiotics, or immune disorders. However, in many cases, the etiology of the disorder is unknown. Sobel¹ suggests that some cases of reinfection may actually be cases of relapse, due to either inadequate testing methods, which result in false-negative results after treatment, or to ineffective treatments. Misdiagnosis of the causative organism may also result in ineffective treatment. The most common causal *Candida* species is *C. albicans*. However, other, less easily eradicated species may also be involved.

Key words: itraconazole, vaginal candidiasis

Itraconazole (Sporanox[®], Janssen Pharmaceuticals) is a triazole with fungistatic activity against *Candida* species, particularly *C. albicans*. Itraconazole reaches high concentrations in tissue due to a high affinity for proteins, particularly keratin.² Active levels of the drug may persist in vaginal epithelium for four days after a one-day treatment.² It has been suggested that a cause of relapse in women with vaginal candidiasis is the re-emergence of *Candida* organisms from deeper layers of vaginal tissue.^{3,4} Oral therapy, unlike topical therapy, may be effective against these "hidden" organisms.

While the majority of cases of vulvovaginal candidiasis are caused by *C. albicans*, some infections are caused by other *Candida* species, including *C. tropicalis* and *C. glabrata*.⁵ An increasing number of infections appear to be caused by these other *Candida* species: 9.9% of cases in 1988 increased to 17.2% in 1995.⁶ Itraconazole may have a greater *in vitro* activity against non-*albicans* species than other azoles, like fluconazole.⁷ Therefore,

itraconazole may be more effective against a broader range of causative organisms.

Clinical Trials

Itraconazole is effective and safe in the treatment of vulvovaginal candidiasis⁸⁻¹⁵ (see Table 1). Treatment regimens of itraconazole 200mg/day for 3 consecutive days^{8,9,11} or 200mg given twice in one day^{9,12,14} have resulted in a high mycological and clinical cure. Studies have also demonstrated mycological cure rates similar to standard treatments, like clotrimazole^{12,13} and fluconazole.^{14,15}

Approximately 5% of women experience recurrent infection, which is defined as at least four episodes in one year, or three episodes known to be unrelated to the use of antibiotics.⁵ Itraconazole may be used prophylactically in order to reduce relapse rates¹⁶⁻¹⁸ (Table 2). Upon cessation of prophylactic treatment, recurrence rates tend to be high in women with a previous history of recurrent vulvovaginal candidiasis.

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Author	Study Design	Regimen (n)	Mycological Cure	Comments (Clinical and Safety Evaluations)
Sanz Sanz, Hernanz ⁹	Randomized dose-finding	<ul style="list-style-type: none"> itraconazole 200mg once/day for 2 consecutive days (n=20) (Group A) itraconazole 200mg twice/day for 1 day (n=20) (Group B) itraconazole 200mg once/day for 3 consecutive days (n=20) (Group C) 	<ul style="list-style-type: none"> mycological cure + disappearance of clinical symptoms (complete cure) 1 week post-treatment: 85% Group A; 65% Group B; 85% Group C mycological cure + disappearance of clinical symptoms (complete cure) 4 weeks post-treatment: 65% Group A; 65% Group B; 83% Group C 	<ul style="list-style-type: none"> disappearance of clinical symptoms but positive mycological cultures (carrier) 1 week post-treatment: 15% Group A; 20% Group B; 5% Group C disappearance of clinical symptoms but positive mycological cultures (carrier) 4 weeks post-treatment: 5% Group A; 12% Group B; 0% Group C 3 adverse events reported in Group C, including mild dyspepsia, burning sensation in stomach, stomach ache
Bloch, et al ¹⁰	Open, prospective, dose-finding	<ul style="list-style-type: none"> itraconazole 100mg twice/day for 1 day (n=30) (Group A) itraconazole 100mg once/day for 2 days (n=32) (Group B) 	<ul style="list-style-type: none"> mycological response 7 days post-treatment: 81% Group A; 83% Group B mycological response 28 days post-treatment: 75% Group A; 63% Group B 	<ul style="list-style-type: none"> no significant differences between groups with respect to clinical signs and symptoms minimal, transient, non-severe side-effects including dizziness, abdominal cramps, nausea, diarrhea and muscle stiffness
Silva-Cruz, et al ¹¹	Randomized, double-blind, placebo-controlled	<ul style="list-style-type: none"> itraconazole 200mg/day for 3 days (n=25) placebo capsules for 3 days (n=25) 	<ul style="list-style-type: none"> mycological cure 1 week post-treatment: % itraconazole; 52% placebo 	<ul style="list-style-type: none"> significant difference between active and placebo groups in clinical signs (pruritus, vaginitis, and vulvitis) one adverse event of epigastric pain reported in the placebo group
Tobin, et al ¹²	Multicentre, single-blind, randomized, parallel-group	<ul style="list-style-type: none"> itraconazole 200mg twice/day for one day (n=109) clotrimazole 500mg vaginal tablet in a single dose (n=105) 	<ul style="list-style-type: none"> mycological cure 1 week post-treatment: 74% itraconazole; 72% clotrimazole mycological cure 6 weeks post-treatment: 51% itraconazole; 50% clotrimazole 	<ul style="list-style-type: none"> significantly, more patients preferred itraconazole treatment to previous treatments received
Stein, Mummaw ¹³	Randomized, controlled	<ul style="list-style-type: none"> itraconazole 200mg/day for 3 days clotrimazole 200mg/day for 3 days placebo 2 capsules per day for 3 days total n=95 with a randomization of 2:1:1 	<ul style="list-style-type: none"> negative mycological cultures 1 week post-treatment: 73% itraconazole; 95% clotrimazole; 32% placebo negative mycological cultures 4 weeks post-treatment: no statistical difference between itraconazole and clotrimazole 	<ul style="list-style-type: none"> clinical success rate 1 week post-treatment: 96% itraconazole; 100% clotrimazole; 77% placebo clinical failure rate 4 weeks post-treatment: 17% itraconazole; 30% clotrimazole (no significant difference [P>0.05; beta=0.81]) minor side-effects: 35% itraconazole; 4% clotrimazole; 41% placebo side-effects with itraconazole included nausea and headache
Woolley, Higgins ¹⁴	Randomized, controlled	<ul style="list-style-type: none"> itraconazole 200mg twice/day for 1 day (n=75) 500mg pessary of clotrimazole with a 1% clotrimazole cream (n=82) fluconazole 150mg once/day for 1 day (n=72) 	<ul style="list-style-type: none"> <i>Candida</i>-negative mycological response 7-10 days post-treatment: 96% itraconazole; 95% clotrimazole; 83% fluconazole 	<ul style="list-style-type: none"> cured clinical response 7-10 days post-treatment: 80% itraconazole; 80% clotrimazole; 62% fluconazole
Mikamo, et al ¹⁵	Randomized, controlled	<ul style="list-style-type: none"> itraconazole 200mg daily for 3 days (n=50) fluconazole single oral 150mg dose (n=50) intravaginal clotrimazole 100mg daily for 6 days (n=50) 	<ul style="list-style-type: none"> complete eradication of <i>Candida</i> species 5-15 days post-treatment: 80% itraconazole; 76% fluconazole; 72% clotrimazole complete eradication of <i>Candida</i> species 30-60 days post-treatment: 74% itraconazole; 70% fluconazole; 60% clotrimazole 	<ul style="list-style-type: none"> clinical effectiveness 5-15 days post-treatment: 92% itraconazole; 80% fluconazole; 72% clotrimazole clinical effectiveness 30-60 days post-treatment: 88% itraconazole; 76% fluconazole; 58% clotrimazole

Table 1: Studies evaluating the efficacy of itraconazole in the treatment of vulvovaginal candidiasis.

Author	Study Design	Regimen (n)	Mycological Cure	Comments (Clinical Cure and Safety)
Creatas, et al ¹⁶	Open	<ul style="list-style-type: none"> • maintenance phase lasting 6 consecutive menstrual cycles of 200mg itraconazole on the first day of menstruation (n=20) 	<ul style="list-style-type: none"> • mycological cure at maintenance phase 6: 20/20 patients (100%) • mycological cure 3 months post-treatment: 17/20 patients (85%) 	<ul style="list-style-type: none"> • clinical results were in total accordance with mycological results • complete cure (clinical and mycological cure) 3 months post-treatment: 85% • no adverse reactions were reported • compliance rate: 100%
Spinillo, et al ¹⁷	Randomized, controlled	<ul style="list-style-type: none"> • itraconazole 200mg twice daily 12 hours apart on the 4th or 5th day of the menstrual cycle for 6 consecutive mos (n=55) • control, i.e., no treatment (n=53) 	<ul style="list-style-type: none"> • mycological recurrences were in accordance with symptomatic recurrences • clinical and mycological recurrence 6 months post-treatment: 36.4% itraconazole; 64.2% control 	<ul style="list-style-type: none"> • symptomatic recurrence during 6 months after cessation of prophylaxis: 38.9% itraconazole; 22.2% control • proportion of patients free of recurrence 1 year post-treatment: 38.9% itraconazole; 28.8% control
Guaschino, et al ¹⁸	Prospective, non-randomized	<ul style="list-style-type: none"> • itraconazole 200mg once daily for 3 days followed by single dose of 200mg the first day of 5 subsequent menstrual cycles (n=11) • boric acid therapy 300mg daily in vaginal ovules of 14 days followed by 300mg daily for 5 days from the first day of 5 subsequent menstrual cycles (n=11) 	<ul style="list-style-type: none"> • positive mycological result at 6 month visit: 1/11 patients (9%) in each group • positive mycological result at 12 month visit (6 months post-treatment): 6/11 patients (54%) in each group 	<ul style="list-style-type: none"> • symptomatic infection at 6 month visit: 4/11 patients (36%) itraconazole; 3/11 patients (27%) boric acid • symptomatic infection at 12 month visit (6 months post-treatment): 6/11 patients (54%) in each group

Table 2: Studies evaluating the efficacy of itraconazole in the prophylactic treatment of vulvovaginal candidiasis.

Conclusion

Itraconazole appears to be an effective treatment for acute and chronic vulvovaginal candidiasis. Oral therapy tends to be shorter in duration than topical therapy. Moreover, patients often prefer oral treatment due to the shorter treatment period and to the ease of administration compared to topical treatments, resulting in increased patient compliance.³ As well, itraconazole used as a prophylactic treatment is a viable option in preventing future recurrence of infection.

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Itraconazole (Sporanox®) for Seborrheic Dermatitis

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ABSTRACT

Seborrheic dermatitis is a common superficial dermatosis, characterized by red, flaking areas of the skin, which may in some cases be covered with yellowish flakes. The most commonly affected areas are the nasolabial folds, ears, eyebrows, scalp and chest. While seborrheic dermatitis may be easy to recognize clinically, the variability of the lesions in both appearance and location may complicate the diagnosis. Seborrheic dermatitis has been described as resembling psoriasis (in which case, the condition may be called "sebopsoriasis") and, when affecting the eyes or ears, has also been described as blepharitis and otitis, respectively. Seborrheic dermatitis tends to be chronic, though seasonal variation is common, with lesions worsening in the dry, winter months.

Key words: itraconazole, seborrheic dermatitis

Seborrheic dermatitis is relatively common, affecting between 1 and 3% of immunocompetent individuals. While the precise etiology of seborrheic dermatitis is not known, endogenous host factors are thought to predispose some people to develop this dermatosis. In particular, yeasts of the genus *Malassezia* (formerly *Pityrosporum orbiculare/ovale*) have been implicated. These yeasts are normal skin commensals, though in some individuals they may cause pityriasis versicolor and *Malassezia folliculitis*. While some investigators have reported that individuals with seborrheic dermatitis have higher *Malassezia* counts on their skin than healthy controls,¹ others have found no difference in *Malassezia* counts between seborrheic dermatitis patients and controls². These authors emphasize instead the importance of host reaction to the yeasts. Much of the evidence for the role of *Malassezia* yeasts is derived partly from treatment studies.

Ketoconazole, an imidazole, is effective against seborrheic dermatitis.^{3,4} The clinical improvement of the lesions is paralleled by a reduction in the number of *Malassezia* yeasts on the skin.^{3,4}

Mechanism of Action

Itraconazole, (Sporanox®, Janssen Pharmaceuticals) a triazole, is highly keratinophilic and lipophilic, and tissue levels of the triazole are several times higher than peak plasma levels.⁵ As a result, itraconazole tends to reach high concentrations in the epidermis and may persist in the skin for 3-4 weeks depending upon the site of infection, thus creating a therapeutic reservoir.⁶ Furthermore, itraconazole does not redistribute into the systemic circulation.⁶ Itraconazole is active against *Malassezia* species *in vitro*⁷ and on excised human stratum corneum.⁸ This triazole may also demonstrate anti-inflammatory activity with inhibition

of 5-lipoxygenase metabolites involved in allergic, inflammatory and immunoreactive processes.⁹⁻¹¹

Clinical Trials

The data obtained from open trials^{9,12,13} (Table 1) suggest that itraconazole may be effective in the treatment of seborrheic dermatitis.

In one study,¹² 30 patients with seborrheic dermatitis of the head (n=10), face (n=10), head and face (n=8), head and extremities (n=1), and chest and thigh (n=1) were treated with itraconazole 150mg or 200mg once per week for 2-3 months. Moisturizers were applied topically. The efficacy of treatment was rated as: markedly effective (3 cases), effective (17), slightly effective (6), not effective (3) and aggravated (1). The efficacy rate was determined by adding cases in which the clinical response was graded as markedly effective or effective (67% of patients). Mycological samples were taken from these patients, but there was no apparent relationship between the presence of *P. ovale* and the clinical course of the disease.

An open trial¹³ evaluated 10 patients with sebopsoriasis of the scalp and face. Eight patients also had lesions of the trunk and extremities. The lesions of sebopsoriasis (lesions of the scalp, eyebrows, ears and seborrheic areas of the trunk) were more inflammatory and eczema-like than most psoriatic lesions. Patients were started on itraconazole 50mg/day for two weeks. If this dosage was well tolerated, the itraconazole was increased to 100mg/day for an additional 4 weeks. Patients were told not to wash their hair for 5 days prior to each assessment of the scalp, and lesions were evaluated using a quadrant-area-severity-scale of 1 (less than 10% involvement) to 5 (greater than 70% involvement). Severity was measured on a 0 - 3 scale, with 0 being "healed". The

Author	Study	Regimen (n)	Outcome
Masataro (1995) ¹²	Open N=30 subjects, most with seborrheic dermatitis of the face and/or head		Itraconazole 150mg or 200mg once weekly for 2-3 months Clinical response was graded as "markedly effective" or "effective" in 67% of patients
Faergemann (1985) ¹³	Open N=10 patients with sebopsoriasis – defined as psoriasis of the scalp, eyebrows, ears and seborrheic areas of the trunk. Lesions appeared more inflammatory and eczema-like than most psoriasis lesions		Itraconazole 50mg/day for 2 weeks: if well tolerated, followed by 100mg/day for an additional 4 weeks 4 patients were cured of scalp lesions and one other patient cured overall. Scalp lesions in general showed the best response. Plaques that had the appearance of classical psoriasis were often unchanged during treatment. Significant (P<0.01) decrease in the number of <i>Malassezia</i> yeasts.
Caputo, et al (2002) ⁹	Open N=160 patients with seborrheic dermatitis		Itraconazole 200mg/day for 7 consecutive days At follow-up 30 days after treatment, clinical improvement was evaluated as: Excellent: 34.3% Good: 40% Moderate: 18.7% Mycological tests positive for <i>Malassezia</i> in 68.7% of patients at baseline. Of these, 46.2% were negative at follow-up The clinical picture in sebopsoriasis patients is intermediate between seborrheic dermatitis and psoriasis. Based on the response to itraconazole (both clinical and in terms of <i>Malassezia</i> yeasts), at least some of the lesions appear to be seborrheic dermatitis rather than psoriasis.

Table 1: Itraconazole in Seborrheic Dermatitis.

total scalp score was obtained by multiplying the total area of the scalp involved by the severity score for the whole scalp. Non-scalp lesions were examined using a 0 - 4 scale. Samples were also taken from the vertex area of the scalp using a detergent scrub technique.¹⁴ Overall, the scalp lesions showed the best response: 4 patients were cured of scalp lesions and one patient was cured overall. The "classic" psoriatic plaques, particularly of the extremities, were often unchanged during treatment. In addition to the clinical improvement shown by these patients, there was a significant (P<0.01) reduction in the number of *P. orbiculare* per cm². No side effects were noted in any patient.

The largest study to date⁹ was an open, single center study involving 160 patients with seborrheic dermatitis. Itraconazole 200mg/day was administered for 7 consecutive days. Patients were evaluated at baseline, day 7 and day 37 following the end of therapy. The parameters evaluated were itching, burning, erythema, desquamation, and each was rated as: absent (0), mild (1), moderate (2), and intense (3). An overall assessment of the degree of improvement was also made by both the physician and the patient at the end of the study. Mycological examination for *Malassezia* yeasts was also performed at baseline, and at days 7 and 37 following therapy.

Two patients discontinued therapy for personal reasons. Improvement in itching was reported in 122 (76.2%) and 130 patients (81.2%) at days 7 and 37, respectively. Burning improved in 84 (52.5%) and 89 (55.6%) patients at days 7 and 37, respectively. There was an improvement in erythema in 112 (70.0%) and 118 (73.7%) patients at days 7 and 37, respectively. Desquamation improved in 128 patients (80%) at day 7, and in 147 patients (91.8%) at day 37. The treatment was judged to be effective by 148 patients (92.5%), with clinicians rating overall improvement as excellent in 55 patients (34.3%), good in 64 patients (40.0%), and moderate in 30 patients (18.7%). Mycological examination (presence of *Malassezia* spores) was positive at baseline in 110 patients (68.7%) and this became negative at day 37 in 74 patients (46.2%).

A maintenance regimen of itraconazole was 200mg/day for the first 2 days of each month. At month 9 following the start of therapy, 28 of 30 patients reported that they had not experienced a relapse. Tolerance and compliance was reported as being excellent. Itraconazole was well tolerated in these studies and this is consistent with previous experience.¹⁵⁻¹⁸

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The Scoring Clinical Index for Onychomycosis (SCIO Index)

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ABSTRACT

Onychomycosis is a common disease, and there are a number of factors that may affect the duration and dosage of treatment including the type of onychomycosis, the area and thickness of nail involvement, the age of the patient, and the location of the digit that is affected. We report a composite index, the Scoring Clinical Index for Onychomycosis (SCIO) that combines these factors to give an index of the overall severity of onychomycosis. The use of the SCIO may have treatment implications; by matching patients with similar SCIO scores, it may be possible to better compare the clinical response to therapy.

Key Words: onychomycosis, hyperkeratosis

Onychomycosis is a common superficial fungal infection, affecting between 6.5 and 12.8% of the population in North America.¹ Individuals over 60 years of age are most commonly affected, with prevalence rates as high as 20-30% in this population.¹ Toenails are involved to a greater extent than fingernails, and the great toenail is the most commonly affected. The clinical presentation of the onychomycosis, i.e., distal and lateral onychomycosis, superficial white onychomycosis, proximal subungual onychomycosis, and total dystrophic onychomycosis must be taken into account when therapeutic decisions are being made. The Scoring Clinical Index for Onychomycosis (SCIO index)

attempts to present the severity of onychomycosis as a composite score.³⁻⁶

The SCIO Index

The clinical pattern component of the SCIO is further divided into (1) clinical form, (2) depth of nail involvement and, (3) thickness of subungual hyperkeratosis. The clinical form is taken from Zaias,² who proposed the classification of onychomycosis into distal-lateral subungual onychomycosis (DLSO), proximal subungual onychomycosis (PSO) and superficial white onychomycosis (SWO). The depth of involvement of the onychomycosis, the degree of hyperkeratosis and the type of clinical presentation are used to calculate SCIO.

Key Factor	Grade 1	Grade 2	Grade 3
Clinical form (f)	DLSO	SWO	PSO
Depth of involvement (d)	<1/3	1/3 to 2/3	>2/3
Degree of hyperkeratosis (h)	absent or < 1mm	1 - 2 mm	> 2 mm

These values are then substituted into the equation:

$$\text{Clinical Index Component} = [(d/3)^{3-f} (f + h(3 - f))]^{1 - [(2 - f)(3 - f)/2]}$$

Using this formula, in SWO, PSO and DLSO the values will be 1, 3, and between 1 and 5, respectively.

The SCIO has a growth component in addition to the clinical index component, and this is based on the location of the onychomycosis (fingernail or toenail, digit number) and the age of the patient.

Key factor	Grade 1	Grade 2	Grade 3
Location (l)	II - V fingernails	Thumbnail or II - V toenails	Big toenail
Age of patient, years (a)	<25	25-60	>60

The growth component may reflect the amount of therapy required for onychomycosis. The growth component value reflects approximately the time needed for complete outgrowth of the target nail. The SCIO index (range 1 to 30) is calculated using the clinical index component and the growth component in the following equation:

$$SCIO = [(d/3)^{3-f} (f + h (3-f)) (1) (a + 3)/3]^{1-[(2-f)(3-f)/2]}$$

A higher SCIO index suggests that the onychomycosis may be more severe and thereby require more prolonged treatment. The proposed guidelines for treatment of onychomycosis according to SCIO values are summarized below:

SCIO	Treatment approach
1-3	Topical treatment: remove (cut or scrape off) affected marginal parts of the nail Use topical antifungals until healthy nail re-grows
3-6	Topical treatment with lower success, which often depends on growth rate Systemic therapy recommended in slower-growing nails or proximal onychomycosis type
6-9	Systemic therapy. Use scheme proposed for fingernails (e.g., itraconazole: 2 pulses of 200mg bid)
9-12	Systemic therapy. Use scheme proposed for toenails (e.g., itraconazole: 3 pulses of 200mg bid)
12-16	Systemic therapy. Use scheme proposed for fingernails with any antifungal (e.g., 4-5 pulses of itraconazole, 200mg bid)
16-20	Combination therapy (systemic antifungal + topical measures) Adequate keratolytic treatment recommended
20-30	Consider nail avulsion (e.g., with urea paste), continue with systemic therapy

To facilitate SCIO evaluation by clinicians, several utilities have been designed. Among them, is the SCIO ruler - a paper device used to obtain the SCIO values without having to make any calculations. The ruler also provides guidelines for selecting treatment strategy in onychomycosis. The same task may be performed with a SCIO electronic calculator or on a special website available at <http://www.onychoindex.com>.

Conclusion

The SCIO may enable comparison of the severity of onychomycosis between nails despite differences in the clinical presentation and demographics. The SCIO index may prove to be an accurate indicator of therapeutic effectiveness. However, further clinical studies will be required before definitive claims can be made.

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Conclusion

The data suggest that itraconazole may be effective and safe in the treatment of seborrheic dermatitis, particularly that present on the face and scalp. Further larger randomized, controlled trials will help confirm these observations.

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