

## Itraconazole and erectile dysfunction

### Introduction

Itraconazole (Trisporal<sup>®</sup>) is a triazole antifungal agent which is registered for treatment of *oropharyngeal candidiasis, dermatomycosis, onychomycosis, pityriasis versicolor, blastomycosis (in immunocompetent patients), histoplasmosis and systemic aspergillosis (in patients who are intolerant of or who are refractory to amphotericin B therapy)*.

Itraconazole has been approved in the Netherlands since 1990 [1].

No impairment of male sexual functions are mentioned in the Dutch SPC of itraconazole yet: neither erectile dysfunction, impotence nor decreased libido [1]. In the USA SPC of itraconazole (Sporanox<sup>®</sup>) impotence and decreased libido are listed as ADRs occurring in clinical trials with an incidence of 1% [2]. Itraconazole possesses structural similarities to ketoconazole (Nizoral<sup>®</sup>) and the mechanism of pharmacological action is similar. Impotence and decreased libido are mentioned in the Dutch SPC of ketoconazole [3]. The Netherlands Pharmacovigilance Centre Lareb has received reports of erectile dysfunction associated with the use of itraconazole.

### Reports

Until September 30, 2005 Lareb received four reports of erectile dysfunction associated with the use of itraconazole, listed in table 1.

Table 1. reports of erectile dysfunction associated with the use of oral itraconazole for onychomycosis.

Patient, age	Dose	Concomitant medication	ADR	Time to onset, outcome
A, 55	2 dd 200 mg pulse	none reported	erection decreased	hours, dechallenge positive (very gradual recovery)
B, 56	2 dd 200 mg pulse	none reported	erectile disturbance	3 days, unknown
C, 57	2 dd 100 mg pulse	lisinopril, atenolol, ibuprofen	erectile dysfunction	unknown, unknown
D, 49	2 dd 100 mg	none reported	erectile dysfunction	2 days, dechallenge positive

In reports A-C so-called "pulse therapy" was used: 3 treatment periods of 2 dd 200mg during one week followed by a 3 week medication-free interval. In patient B the erectile disturbance persisted during the medication-free interval. Patient C was treated with tadalafil 10 mg without success. Patient D had also experienced erectile dysfunction during previous treatment with terbinafine.

No cases of erectile dysfunction have been reported to Lareb in association with the use of ketoconazole.

## Other sources of information

### Literature

A literature search revealed a few reports in which impotence and a decrease in libido have been reported during oral itraconazole therapy [4-6]. Impotence and a decrease in libido were reported with incidences of 0.5% and 1% in one case series of patients with systemic mycoses [6]. No reports on erectile dysfunction as adverse drug reaction of itraconazole were discovered.

Evans *et al.* describe off label use of high dose ketoconazole to prevent postoperative erections in patients who underwent urological surgery [7].

### Databases

The database of the Uppsala Monitoring Centre of the WHO contains no reports of erectile dysfunction in association with the use of itraconazole or ketoconazole. However there are several reports of impotence and decreased libido: these associations are disproportionately present in the WHO database. Although impotence is not listed in the SPC of itraconazole the disproportionality is even stronger with itraconazole than with ketoconazole.

Table 2. reports of impotence associated with itraconazole of ketoconazole in the WHO database

drug	Impotence	ROR (95% CI)
itraconazole	54	2.27 (1.74 – 2.97)
ketoconazole	32	1.52 (1.09 – 2.19)

### Mechanism

The mechanism of itraconazole induced sexual disorders is unknown. The literature does not support a similar interference with testosterone synthesis as described for ketoconazole. The mechanism of the antifungal action of itraconazole, like ketoconazole, involves prevention of ergosterol synthesis in fungal cell membranes via inhibition of cytochrome P450. This inhibition causes ketoconazole to reversibly inhibit testosterone synthesis. Itraconazole, compared to ketoconazole, has a much higher affinity for fungal cytochrome P450 and binds only weakly to human P450 enzymes. In a study of limited size no clinical or laboratory evidence of impaired human testosterone synthesis could be found in patients treated with itraconazole [8].

### Conclusion

Lareb received reports of sexual dysfunction specified as erectile dysfunction associated with the use of oral itraconazole for onychomycosis. In two of these reports dechallenge was positive. Sexual dysfunction specified as impotence is disproportionately present in the WHO database in association with both itraconazole and ketoconazole. Impotence is listed in the Dutch SPC of ketoconazole, in the USA SPC of itraconazole and is reported in the literature. According to the Marketing Authorization holder, these ADRs will be reported in the Dutch SPC in the course of 2006

## References

1. Dutch SPC of Trisporal® (versiondate 06-08-2002, access date 06-09-2005) <http://www.cbg-meb.nl/IB-teksten/13224.pdf>
2. USA SPC of Sporanox® (versiondate jan 2004, access date 06-09-2005) [http://www.janssen.com/active/janus/en\\_US/assets/common/company/pi/sporanox.pdf](http://www.janssen.com/active/janus/en_US/assets/common/company/pi/sporanox.pdf)
3. Dutch SPC of Nizoral® (versiondate 21-06--2004, access date 06-09-2005) <http://www.cbg-meb.nl/IB-teksten/08938.pdf>
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6. Tucker RM, Haq Y, Denning DW et al: Adverse events associated with itraconazole in 189 patients on chronic therapy. *J Antimicrob Chemother* 1990a; 26:561-566.
7. Evans KC, Peterson AC, Ruiz HE, Costabile RA. Use of oral ketoconazole to prevent postoperative erections following penile surgery. *Int J Impot Res.* 2004 Aug;16(4):346-9. *J*
8. Queiroz-Telles F, Purim KS, Boguszewski CL, Afonso FC, Graf H. Adrenal response to corticotrophin and testosterone during long-term therapy with itraconazole in patients with chromoblastomycosis. *J Antimicrob Chemother.* 1997 Dec;40(6):899-902.