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## Itraconazole and paresthesias

### Introduction

Itraconazole (Trisporal<sup>®</sup>) is a triazole antifungal agent which has been approved for the Dutch market in 1988. The gastro-intestinal and hepatobiliary adverse drug reactions are the most common. With long term use, also peripheral neuropathy has been described [1]. However, short term use appears to be associated with paresthesia. It is unclear whether this paresthesia with such remarkable short latency time is a first sign of peripheral neuropathy. Itraconazole induced paresthesia with such short latency time is not mentioned in the SPC [2].

### Reports

On February 8, 2004 the database of the Netherlands Pharmacovigilance Centre contained 18 reports concerning paresthesias associated with the use of itraconazole. The latency period for these reports was in most cases short, only one to several days.

In addition Lareb received 12 reports concerning (poly)neuropathy, but only in three of these cases neural damage was confirmed by a neurologist. First symptoms in these confirmed reports have been tingling sensations and numbness in feet, legs, hands and arms. Latency time varied from a few weeks to 8 months. No cases of paresthesias or neuropathy on other triazole derivatives (voriconazole, fluconazole, terconazole) are present in the database.

### Other sources of information

#### Literature

A literature search reveals no relevant publications of paresthesias or peripheral neuropathy in combination with the use of itraconazole or other triazoles. In the general population, peripheral neuropathy is quite common with a prevalence of 2.4% [3]. Because it can be disabling or fatal, early diagnosis is important. The most common causes of acute generalized peripheral neuropathy are vasculitis, diabetes mellitus, critical illness or drugs. First symptoms of neuropathy are (distal) paresthesias, altered sensation and weakness. Most peripheral neuropathies are chronic and usually develop over several months [3].

#### Databases

The association itraconazole and paresthesias is disproportionally present in both the Lareb and the database of the WHO Uppsala monitoring centre (table 2).

Table 2. Overview of data of case/non-case approach of Lareb and WHO database

Database	itraconazole and paresthesias	itraconazole total	ROR (95% CI)
Lareb	18	282	4.2 (2.6 – 6.9)
WHO	119	5667	1.4 (1.1 – 1.6)

#### Mechanism

The mechanism of itraconazole induced paresthesias is unknown. Taking into account the short latency time, we presume a direct neurotoxic mechanism. However no data could be found to support this hypothesis.

*Prescription data*

Total number of prescriptions of itraconazole are shown in table 3.

Table 3. Total number of prescriptions of itraconazole per year since 1999 (Source: GIP College voor Zorgverzekeringen, Diemen).

	1999	2000	2001	2002	2003
J02AC02 Itraconazol	177.000	187.000	173.000	157.000	151.000

**Conclusion**

Lareb received 18 reports of paresthesias in association with itraconazole. Most cases have a remarkable short latency of a few days after start. Paresthesias are disproportionately associated with itraconazole in both the WHO and Lareb databases.

Paresthesias are not mentioned in the SPCs of itraconazole.

References

1. KNMP; 2004; Informatarium Medicamentorum 2004
2. Dutch SPC Trisporal®. (version date 06-08-2002) <http://www.cbg-meb.nl/IB-teksten/13224.pdf>
3. Hughes RAC. Clinical review: Peripheral neuropathy. BMJ 2002; 324:466-469