

**Public Assessment Report**  
**for paediatric studies submitted in accordance**  
**with Article 45 of Regulation (EC) No1901/2006, as amended**

**Itraconazole**

**EE/W/0004/pdWS/001**

<b>Rapporteur:</b>	Estonia
<b>Finalisation procedure (day 120):</b>	26.11.2010
<b>Date of finalisation of PAR</b>	

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VI
INN (or common name) of the active substance(s):	Itraconazole
MAH (s):	Johnson&Johnson
Pharmaco-therapeutic group (ATC Code):	J02AC02
Pharmaceutical form(s) and strength(s):	Capsules, hard 100mg; oral solution 10mg/ml; concentrate and solvent for solution for infusion 10mg/ml

## I. EXECUTIVE SUMMARY

Itraconazole is an antimycotic for systemic use, a triazole derivative. Itraconazole impairs the synthesis of ergosterol in fungal cells which is a vital membrane component in fungi. Impairment of its synthesis results in an antifungal effect. Itraconazole is effective in infections due to dermatophytes (*Trichophyton* spp., *Microsporum* spp., *Epidermophyton floccosum*), yeasts (*Cryptococcus neoformans*, *Pityrosporum* spp., *Candida* spp., including *C. albicans*, *C. glabrata* and *C. krusei*), *Aspergillus* spp., *Histoplasma* spp., *Paracoccidioides brasiliensis*, *Sporothrix shenckii*, *Fonsecaea* spp., *Cladosporium* spp., *Blastomyces dermatitidis* and various other fungi and yeasts. Currently, there are 3 formulations: capsules, oral solution and IV solution.

Itraconazole is authorized for the treatment of adults only. Since clinical data on the use of Itraconazole in paediatric patients is limited, its use in children is not recommended, unless the potential benefit outweighs the potential risks. In the SPC of itraconazole oral solution in section 4.2 information about paediatric posology is included: *Prophylaxis of fungal infections: there are no efficacy data available in neutropenic children. Limited safety experience is available with a dose of 5 mg/kg per day administered in two intakes. The incidence of adverse events such as diarrhoea, abdominal pain, vomiting, fever, rash and mucositis was higher than in adults.*

MAH proposed no SmPC and PL changes.

Based on the review of the presented paediatric data in the day 70 preliminary PdAR the rapporteur concluded the data from the submitted studies did not justify new indications but focused on wording for dosage recommendation and specific safety information related to paediatric patients in sections 4.2, 4.8, 5.1 and 5.2 of the SmPC. The response from the MAH was received in September 2010 and included the MAH's response to the comments raised in the Preliminary Paediatric Assessment Report and by the CMS. An amended version of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC was endorsed by the CMSs.

## II. RECOMMENDATION<sup>1</sup>

Based on responses from the MAH and comments from MSs, the following specific wording related to paediatric use is proposed for sections 4.2, 4.8, 5.1 and 5.2 of the SmPC.

### 4.2 Posology and Method of Administration

#### *Use in children*

Since clinical data on the use of SPORANOX Oral Solution in paediatric patients is limited, its use in children is not recommended unless the potential benefit outweighs the potential risks (see Section 4.4).

Prophylaxis of fungal infections: there are no efficacy data available in neutropenic children. Limited safety experience is available with a dose of 5 mg/kg per day administered in two intakes (see Section 4.8).

### 4.8 Undesirable Effects

#### *Paediatric Population*

The safety of SPORANOX oral solution was evaluated in 250 paediatric patients aged 6 months to 14 years who participated in five open-label clinical trials. These patients received at least one dose of SPORANOX oral solution for prophylaxis of fungal infections or for treatment of oral thrush or systemic fungal infections and provided safety data. Based on pooled safety data from these clinical trials, the very common reported ADRs in paediatric patients were Vomiting (36.0%), Pyrexia (30.8%), Diarrhoea (28.4%), Mucosal inflammation (23.2%), Rash (22.8%), Abdominal pain (17.2%), Nausea (15.6%), Hypertension (14.0%), and Cough (11.2%). The nature of ADRs in paediatric patients is similar to that observed in adult subjects, but the incidence is higher in the paediatric patients.

---

<sup>1</sup> The recommendation from section V can be copied in this section.

## **5.1 Pharmacodynamic Properties**

### *Paediatric Population*

The tolerability and safety of itraconazole oral solution was studied in the prophylaxis of fungal infections in 103 neutropenic paediatric patients aged 0 to 14 years (median 5 years) in an open-label uncontrolled phase III clinical study. Most patients (78%) were undergoing allogeneic bone marrow transplantation for haematological malignancies. All patients received 5 mg/kg/day of itraconazole oral solution as a single or divided dose. Due to the design of the study, no formal conclusion with regard to efficacy could be derived. The most common adverse events considered definitely or possibly related to itraconazole were vomiting, abnormal liver function, and abdominal pain.

## **5.2 Pharmacokinetic Properties**

### Special Populations

#### *Paediatric Population*

Two pharmacokinetic studies have been conducted in neutropenic children aged 6 months to 14 years in which itraconazole oral solution was administered 5 mg/kg once or twice daily. The exposure to itraconazole was somewhat higher in older children (6 to 14 years) compared to younger children. In all children, effective plasma concentrations of itraconazole were reached within 3 to 5 days after initiation of treatment and maintained throughout treatment.

## **III. INTRODUCTION**

Johnson & Johnson submitted 5 completed paediatric studies for itraconazole, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. Neutropenic children received 4.5 to 5.5 mg/kg/day itraconazole as oral solution and 2 mg/kg was given to infants with oral thrush. Duration of treatment was 1 to 10 days for oral thrush and 13 to 50 days in neutropenic children. The trials were conducted 1990 - 1998.

No line-listing of presently nationally approved indications, dosage regimens or safety information for paediatric use of itraconazole has been provided.

No clinical expert overview has been provided.

The MAH stated that based on the review of the available data, no amendment to the existing SPC is needed. Taking into account the rapporteur's and NL recommendations, the MAH proposed the amendments to the SPC.

## **IV. SCIENTIFIC DISCUSSION**

### **IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)**

Currently, there are 3 formulations: capsules, oral solution and IV solution. In submitted studies itraconazole oral solution was used.

### **IV.2 Non-clinical aspects**

No data are provided

### **IV.3 Clinical aspects**

**An open evaluation of itraconazole oral solution in paediatric patients undergoing treatment for haematological malignancy or solid tumour. A tolerability, efficacy and safety evaluation**

This was an open study of oral antifungal prophylaxis in 103 neutropenic paediatric patients aged 0-14 years (median 5 years). Most (78%) were undergoing allogeneic bone marrow transplantation for haematological malignancies. All patients received 5mg/kg/day of itraconazole liquid (10mg/ml HP-β-CD solution) as a single or divided dose. Where possible prophylaxis was started at least 7 days prior to the onset of neutropenia and continued until neutrophil recovery. Of the 103 children who entered the study, 47 completed the course of prophylaxis, 27 withdrew because of poor compliance, 19 for adverse events and 10 for other reasons. Two patients died during the study and a further 5 within 30 days of the last dose of study medication. No proven systemic infections occurred during the study but 26 patients received intravenous amphotericin for antibiotic unresponsive pyrexia. Three patients developed suspected oral candidosis but these were not confirmed mycologically and no treatment was given. One patient developed mycologically confirmed oesophageal candidosis and was treated with parenteral amphotericin. Serious adverse events were reported in 27 patients including convulsions (7), drug interactions (6), abdominal pain (4) and constipation (4). The most common adverse events considered definitely or possibly related to itraconazole were vomiting (12), abnormal liver function (5) and abdominal pain (3). Tolerability of study medication at study end-point was rated as good (55%), moderate (11%), poor (17%) and unacceptable (17%). Some patients had poor oral intake due to mucositis. No unexpected problems of safety or tolerability were encountered in this study. The changes observed in the haematological and biochemical laboratory parameters were considered inherent to the patient population studied.

#### **Assessor's comment**

*As the study was open and not randomised, no formal conclusions cannot be drawn. But as no proven systemic and only one mucosal infection occurred, Itraconazole oral solution can be used as antifungal prophylaxis in neutropenic children.*

#### **Pharmacokinetic study of itraconazole oral solution during chronic treatment in neutropenic children**

The pharmacokinetics of itraconazole oral solution formulated in hydroxypropyl-β-cyclodextrin (HPβCD) was determined for two groups of neutropenic children without allogeneic bone marrow transplant. This was an open, multicentric phase II trial in 20 neutropenic children divided in two groups (Group 1 aged between 1.7 and 4.9 years, n=10, Group 2 aged between 6.2 and 14.3 years, n=7). Trial was run from 06 May to 24 Jan 96. Three subjects dropped out before trial completion for the following reasons: poor compliance, coma, mucositis. Children received 4.5 to 5.5 mg/kg/d (mean 4.9±0.2) in group 1 and 4.9 to 5.4mg/kg/d (mean 5.1±0.16) in group 2 administered BID during the period of neutropenia, starting seven to ten days before the expected first day of neutropenia and ending two days after the end of neutropenia unless the investigator decided to stop itraconazole because of a clinical condition requiring amphotericin B IV. The first administration was taken the morning before the breakfast, and the second administration before the dinner. Before each morning drug administration, subjects were fasting since at least 12 hours. Treatment duration was 13 to 50 days in group 1 (mean 35 days) and 8 to 47 days in group 2 (mean 31 days). Through concentrations of itraconazole and hydroxyl-itraconazole ( $H_0$ ) were determined by HPLC every other day of the treatment, at the end of neutropenia ( $D_{EN}$ ) and 2 days after the end of neutropenia ( $D_{EN+2}$ ). The urinary concentrations of itraconazole (ITR), hydroxyl-itraconazole (OH-ITR) and HPβCD were measured from 0 to 24 h at  $D_7$  and  $D_{11}$ . An area under the curve concentration/time was calculated from the trough plasma concentrations ( $H_0AUC_{24}$ ) and standardized to 24 hours. The results show that satisfactory plasma levels were obtained either on the third (for the second group) or on the fifth day (for the first group) of treatment and maintained up to the end of neutropenia: for ITR  $H_0D_5=351\pm172$  ng/ml and  $H_0D_3=328\pm98$  ng/ml for group 1 and group 2 respectively,  $H_0D_{15}=711\pm251$  and  $1072\pm408$  ng/ml for group 1 and group 2 respectively; for OH-ITR,  $H_0D_5=732\pm335$  ng/ml and  $H_0D_3=700\pm121$  for group 1 and 2 respectively,  $H_0D_{15}=1275\pm322$  and  $1964\pm562$  ng/ml in group 1 and group 2 respectively. Only one dosage was evaluated to confirm in children the bioavailability of the adult recommended dosage (5mg/kg/d).

**Assessor's comment**

*The results of the present trial demonstrate that the therapeutic level was reached between three and five days after initiation of treatment and was maintained up to the end of neutropenia. Comparatively to adult neutropenic patients treated with similar dosage (5,8 mg/kg/d) of oral solution in another study, the plasma levels appear superior in children. Studies in healthy volunteers have shown that the overall bioavailability of the new oral solution formulation is 30% higher than that of the capsule formulation and that the bioavailability is optimum when oral solution is taken in fasting conditions. The bioavailability of itraconazole oral solution appears satisfactory in neutropenic children.*

**Evaluation of itraconazole solution in infants with oral thrush: a multicentre trial comparing four different treatment durations**

This study was a synoptic clinical research report of multicentral, randomized, open parallel group clinical phase II trial. Indication: Oral thrush to determine the duration in infants with the oral solution of itraconazole (2mg/kg body weight, o.d.; following a meal) comparing a 1 day to 3 day and 7 day course. No of subjects 74, male and female patients with a maximum age of 2 years, with white spots inside the mouth and Candida was documented inside the mouth by a positive culture and microscopy.

**Main features of the trial sample and summary of the results**

Baseline characteristics-subject disposition	One day	Three days	Five days	Seven days
Number of subjects entered (M/F)	25 (14/11)	26 (15/11)	21 (9/12)	2 (1/1)
Age: median (min-max), days	48 (7-814)	60 (6-818)	110 (9-518)	60 (30-90)
Drop-outs	0	0	0	0

Safety (n=number of subjects with data)	One day (n=25)	Three days (n=26)	Five days (n=21)	Seven days (n=2)
Adverse events (AE)	Vomiting		Taste perversion	
No. (%) with one or more AE	1(4)	0	1(5)	0
No. (%) of deaths	0	0	0	0
No. (%) with one or more other serious AE	0	0	0	0
No (%) treatment stopped due to AE	0	0	0	0
Clinical laboratory parameters	Not applicable	Not applicable	Not applicable	Not applicable

**Conclusion:** The results of the present trial demonstrate that adverse events were reported in only 3% of the patients. Therefore, itraconazole is considered to be clinically safe and generally well tolerated in infants.

**Assessor's comment**

*The indication of the study was to determine the duration of treatment in infants with the oral solution of itraconazole (2mg/kg body weight, o.d.; following a meal) comparing a 1 day to 3 day and 7 day course, but the study does not provide any data on efficacy of different treatment regimen. The study confirms that itraconazole is effective in the treatment of oral thrush in children up to 2 years.*

**Repeated dose pharmacokinetics of itraconazole in oral solution, 5mg/kg once daily for two weeks, in infants and children**

This was an open multicentre trial (clinical phase III) to investigate the safety, tolerability and pharmacokinetics of itraconazole in oral solution, 5mg/kg once daily for two weeks, in children requiring systemic antifungal treatment. The trial was run from 3 June 1994 to 14 July 1995. In total, 26 patients

were recruited. Eight patients belonged to the (6 months, 2 yrs) group, 7 patients to the (2yrs, 5yrs) group and 11 patients to the (5yrs, 12yrs) group. During the open treatment period, 3 patients in the (5yrs, 12yrs) group dropped out, two of them due to adverse events (fever, which was considered as a prophylactic end point), the other one was not cooperative. In addition, one patient discontinued the treatment (but continued to have assessments) due to an adverse event (vomiting). During the run-out period, one patient in the (6 months, 2yrs) group dropped out due to an intercurrent event (moved). *Itraconazole was administered as an oral solution containing 10mg/ml itraconazole and 400 mg/ml hydroxypropyl-β-cyclodextrin (HP-β-CD) provided in vials containing 100 ml of the solution.* Blood samples were taken at regular time points after the first dose, during treatment and up to 8 days after the last itraconazole dose. Whenever possible, urine was collected during 24 h after the first and last dose to determine the oral bioavailability of HP-β-CD, the solubilizer of itraconazole in the oral solution.

On day 1, the mean values of  $C_{max}$  and  $AUC_{0-24h}$  of itraconazole and hydroxy-itraconazole and their metabolic ratio were lower in the 6 months-2 years age group compared to the other two groups. However on day 14,  $C_{max}$ ,  $AUC_{0-24h}$  and metabolic ratio were comparable in the three age groups for both itraconazole and hydroxy-itraconazole.  $C_{max}$  and  $AUC_{0-24h}$  markedly increased from day 1 to day 14. The mean  $AUC_{0-24h}$ - based accumulation factors of itraconazole and hydroxy-itraconazole for the three age categories ranged from 3.3 to 8.6 and from 2.3 to 11.4, respectively. On day 14, the mean itraconazole and hydroxy-itraconazole  $C_{max}$  ranged from 534 to 631ng/ml and 687 to 699 ng/ml, the itraconazole and hydroxy-itraconazole  $AUC_{0-24}$  ranged from 6.93 to 8.77 $\mu$ .h/ml and 13.2 to 13.5  $\mu$ .h/ml, and the metabolic ratio from 1.7 to 2.1 respectively. The  $T_{max}$  and  $t_{1/2term}$  were comparable in three groups. Median  $T_{max}$  of itraconazole on day 14 ranged from 1.9 to 2 hours. Mean (median)  $t_{1/2term}$  of itraconazole on day 14 for the 6 months-2 years, 2 years-5 years and 5 years-12 years age groups were 47.4 (24.6), 30.6 (21.1) and 28.3 (30.8) h, respectively. For hydroxy-itraconazole, the mean (median)  $t_{1/2term}$  were 18 (8.3), 17.1 (9.7) and 17.9 (17.7) h, respectively. There was a tendency to lower  $C_{min}$  for both itraconazole and hydroxy-itraconazole in the 6 months – 2 years, 2 years – 5years and 5 years – 12 years age groups were 159 (64.9), 179 (187) and 223 (204) ng/ml, respectively. For hydroxy-itraconazole, the mean (median)  $C_{min}$  were 308 (89.2), 487 (423) and 437 (526) ng/ml, respectively.

The oral bioavailability of HP-β-CD estimated from urinary excretion data was less than 1% in the majority of the patients.

During the open treatment period, adverse events - mainly gastrointestinal system and general disorders - were reported in all patients, except for two in the 6 months - years group. During the run – out period, adverse events were reported in two patients in the 6 months – 2 years group, five patients in the 2 years – 5 years group and six patients in the 5 years – 12 years group. The most frequently reported adverse event was vomiting; it was noted in one, five, and seven patients respectively, during open treatment, and in two patients in both the (2 yrs, 5yrs) group and the (5 yrs, 12 yrs) group during the run-out period. Two patients in the 5 years – 12 years group stopped the treatment because of fever. The median values of haematology and biochemistry did not show consistent, clinically relevant changes. There were relatively many important laboratory abnormalities, but these could be accounted for this patient population.

**In conclusion**, itraconazole and hydroxyl-itraconazole pharmacokinetics were comparable in the three age groups except that  $C_{max}$ ,  $AUC_{0-24}$  and  $ratio_{met}$  after the first dose and  $C_{min}$  during the repeated administration tended to be lower in the 6 months – 2 years age group. However, in contrast to the other age groups, the 6 months – 2 years group was mainly composed of liver transplant patients.

#### **Assessor's comment**

*The conclusion of the applicant is supported. Itraconazole dosed at 5mg/kg once daily as an oral solution for two weeks can be considered well tolerated and safe in infants and children.*

#### **Evaluation of itraconazole oral solution in infants with oral thrush: an open trial comparing three, five or seven days of treatment with ten days of nystatin treatment**

This study was a synoptic clinical research report of single centre, open, four parallel groups, active control (nystatin), and clinical phase II trial.

Indication/objectives: oral thrush/ to evaluate the efficacy and to assess the safety of itraconazole oral solution for three, five or seven days in comparison with nystatin suspension for ten days.

Inclusion criteria: body weight does not exceed 10 kg

White spots inside the mouth

At least two intra-oral signs and symptoms, related to oral thrush

Candida albicans documented (by microscopy) inside the mouth

Exclusion criteria: inability to receive oral medication

Systematic antifungal therapy within the past two weeks or intra-oral antifungal therapy within the past week

Peri-oral lesions only

Concomitant administration of other antifungal treatment

Treatment: itraconazole solution 2 mg/kg (i.e. 0.2 ml/kg) b.i.d.; nystatin suspension 100.000 units q.i.d.

Duration of treatment 3, 5, 7 or 10 days, duration of trial max 11 days

### Main features of the trial sample and summary of the results

Baseline characteristics –patient disposition	Itraconazole (3 days)	Itraconazole (5 days)	Itraconazole (7 days)	Nystatin (10 days)
Number of patients entered (M/F)	10 (8/2)	10 (5/5)	10 (7/3)	11 (6/5)
Age: median (min-max), months	7.0 (1-56)	1.5 (0-8)	2.5 (0-73)	4.0 (0-36)
Drop-outs-reason <ul style="list-style-type: none"> <li>• Death</li> <li>• Investigator incapacitation</li> </ul>			1	1
Relevant concurrent medications <ul style="list-style-type: none"> <li>• Carbamazepin</li> <li>• Phenytoin</li> <li>• Phenobarbital</li> </ul>	1 1 2			2
Total no (%) of patients taking one or more concurrent medications	7 (70%)	8 (80%)	9 (90%)	9 (82%)

Effectiveness (n=number of patients with data)	Itraconazole (3 days) (n=10)	Itraconazole (5 days) (n=10)	Itraconazole (7 days) (n=10)	nystatin (10 days) (n=11)
Primary variable Clinical response, i.e., all symptoms related to oral thrush (sprue, erythema, perlèche and cheilitis) absent at end point, n/n assessed (%)	7/10 (70%)	10/10 (100%)	9/10 (90%)	1/11 (9%)
Secondary variables Signs and symptoms: severity score absent/mild/moderate/severe, n				
-sprue				
baseline	10/0/0/0	7/1/1/1	6/3/0/1	8/1/2/0
end point	10/0/0/0	10/0/0/0	10/0/0/0	10/1/0/0
-erythema				
baseline	2/4/3/1	0/4/4/2	1/7/2/0	0/5/6/0
end point	9/1/0/0	10/0/0/0	10/0/0/0	8/3/0/0
-perlèche				
baseline	0/1/8/1	0/0/9/1	0/3/6/1	0/2/5/4
end point	7/2/1/0	10/0/0/0	9/1/0/0	2/7/2/0
-cheilitis				
baseline	5/5/0/0	7/3/0/0	7/3/0/0	6/5/0/0
end point	10/0/0/0	10/0/0/0	10/0/0/0	10/1/0/0
Global evaluation: cured/markedly				

improved/moderately improved/unevaluable at end point, n	8/0/2/0***	10/0/0/0	8/1/0/1	1/0/9/1
--	------------	----------	---------	---------

Asterisks refer to comparison between four groups (for clinical response and global evaluation)

Level of significance:\*\*\*p≤0.001

Safety (n=number of patients with data)	Itraconazole (3 days) (n=10)	Itraconazole (5 days) (n=10)	Itraconazole (7 days) (n=10)	nystatin (10 days) (n=11)
Adverse events (AE)				
-diarrhoe				3
-pharyngitis				1
-sepsis				1
No. (%) with one or more AE	0	0	0	4 (36%)
No. (%) of deaths				1 (9%)
No. (%) treatment stopped due to AE				2 (18%)

**Conclusions: The results of the presented trial were as expected, although a statistically significant intergroup difference, in favour of itraconazole, was not anticipated. Even though most infants in this trial were severely ill, the current development plan for itraconazole oral solution does not support its use in non-immunocompromised patients. Further follow-up trials are not planned.**

**Assessor's comment**

*Itraconazole oral solution is effective and safe in infants and children with oral thrush.*

## V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Overall the proposed changes in the SmPC of itraconazole should reflect the paediatric information available. Based on the review of the presented paediatric data the rapporteur considers that the following specific wording related to paediatric use is proposed for sections 4.2, 4.8, 5.1 and 5.2 of the SmPC.

### 4.2 Posology and Method of Administration

#### *Use in children*

Since clinical data on the use of SPORANOX Oral Solution in paediatric patients is limited, its use in children is not recommended unless the potential benefit outweighs the potential risks (see Section 4.4).

Prophylaxis of fungal infections: there are no efficacy data available in neutropenic children. Limited safety experience is available with a dose of 5 mg/kg per day administered in two intakes (see Section 4.8).

### 4.8 Undesirable Effects

#### *Paediatric Population*

The safety of SPORANOX oral solution was evaluated in 250 paediatric patients aged 6 months to 14 years who participated in five open-label clinical trials. These patients received at least one dose of SPORANOX oral solution for prophylaxis of fungal infections or for treatment of oral thrush or systemic fungal infections and provided safety data. Based on pooled safety data from these clinical trials, the very common reported ADRs in paediatric patients were Vomiting (36.0%), Pyrexia (30.8%), Diarrhoea (28.4%), Mucosal inflammation (23.2%), Rash (22.8%), Abdominal pain (17.2%), Nausea (15.6%), Hypertension (14.0%), and Cough (11.2%). The nature of ADRs in paediatric patients is similar to that observed in adult subjects, but the incidence is higher in the paediatric patients.

## **5.1 Pharmacodynamic Properties**

### *Paediatric Population*

The tolerability and safety of itraconazole oral solution was studied in the prophylaxis of fungal infections in 103 neutropenic paediatric patients aged 0 to 14 years (median 5 years) in an open-label uncontrolled phase III clinical study. Most patients (78%) were undergoing allogeneic bone marrow transplantation for haematological malignancies. All patients received 5 mg/kg/day of itraconazole oral solution as a single or divided dose. Due to the design of the study, no formal conclusion with regard to efficacy could be derived. The most common adverse events considered definitely or possibly related to itraconazole were vomiting, abnormal liver function, and abdominal pain.

## **5.2 Pharmacokinetic Properties**

### Special Populations

#### *Paediatric Population*

Two pharmacokinetic studies have been conducted in neutropenic children aged 6 months to 14 years in which itraconazole oral solution was administered 5 mg/kg once or twice daily. The exposure to itraconazole was somewhat higher in older children (6 to 14 years) compared to younger children. In all children, effective plasma concentrations of itraconazole were reached within 3 to 5 days after initiation of treatment and maintained throughout treatment.

A type IB variation to update the SmPC in line with the above work-sharing recommendations will be requested from the MAHs within 60 days after finalising this procedure.

#### ➤ **Overall conclusion**

Itraconazole is an antimycotic for systemic use in adults. Since clinical data on the use of Itraconazole in paediatric patients is limited, no clear recommendation on paediatric use should be included in section 4.1. The specific wording related to paediatric use is proposed for sections 4.2, 4.8, 5.1 and 5.2 of the SmPC.

#### ➤ **Recommendation**

A type IB variation will be requested from the MAH within 60 days after finalising this procedure.

## **VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED**

*The list can be taken from the spreadsheet compiled from the EMA.*