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

Ketoconazole-containing tablets, shampoo and cream

Ketoconazole

DK/W/0012/pdWS/001

Rapporteur:	DK
Finalisation procedure (day 120):	19-12-2012
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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Nizoral Oronazol Fungoral Ketode
INN (or common name) of the active substance(s):	Ketoconazole
MAH (s):	Johnson & Johnson Janssen-Cilag
Pharmaco-therapeutic group (ATC Code):	D 01 AC 08 J 02 AB 02
Pharmaceutical form(s) and strength(s):	Shampoo 2% Cream 2% Tablets 200 mg

I. EXECUTIVE SUMMARY

SmPC changes are proposed in sections 4.2 and 5.2.

Summary of outcome

☐ No change

☒ Change

☐ New study data: <section(s) xxxx, xxxx>

☐ New safety information: <section(s) xxxx, xxxx>

☒ Paediatric information clarified: section(s) 4.2, 5.2.

☐ New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION[1]

Ketoconazole 200 mg tablets

Efficacy and safety of oral ketoconazole in paediatric patients has not been documented in the submitted clinical studies. Therefore the suggested posology in children cannot be recommended.

Recommendations for use of oral ketoconazole in paediatric patients are also inappropriate at present due to the ongoing Article 31 Referral questioning the safety, i.e. hepatotocicity, of oral ketoconazole in treated patients.

Ketoconazole shampoo 2%

Due to lack of pharmacokinetics as well as efficacy and safety data use of ketoconazole shampoo 2% is not recommended in infants and children.

Ketoconazole shampoo 2% has been shown to be effective and safe in adolescents with seborrheic dermatitis and pityriasis versicolor.

Therefore the following wording in SPC 4.2 is acceptable:

SPC 4.2
Ketoconazole shampoo 2% is for use in adolescents and adults.

[1] *The recommendation from section V can be copied in this section*.

Ketoconazole cream 2%

The data on efficacy (n =19) and safety (n=7) of ketoconazole cream 2% is considered insufficient for approval in paediatric use.

Therefore only the following wording in SPC 4.2 is acceptable:

SPC 4.2
Ketoconazole cream is for use in adults.

The MAH has submitted supplementary pharmacokinetic data in children exposed to ketoconazole cream 2% which is found to be appropriate.

Therefore the following wording in SPC 5.2 is acceptable:

SPC 5.2
Plasma concentrations of ketoconazole were not detectable after topical administration of Nizoral 2% cream in adults on the skin. In one study in infants with seborrhoeic dermatitis (n=19), where approximately 40 g of Nizoral 2% cream was applied daily on 40% of the body surface area, plasma levels of ketoconazole were detected in 5 infants, ranging from 32 to 133 ng/ml.

III. INTRODUCTION

The MAH has submitted available clinical studies for the use of ketoconazole tablets, cream and shampoo 2% in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided (Report Date: 25 April 2011)

The MAH proposed the following regulatory action:

Ketoconazole 200 mg tablet

SPC 4.2

Children
- Children weighing from 20-40 kg: One half a tablet (= 100 mg) once daily with a meal.
- Children weighing more than 40 kg: Same as for adults.

Administration of Ketoconazole in children weighing < 20 kg is not recommended, as the 200 mg tablets are not scored to dispense < 100 mg.

Ketoconazole shampoo 2%

SPC 4.2

Ketoconazole (trade name) shampoo 2% is for use in infants, children, adolescents and adults.

Ketoconazole cream 2%

Ketoconazole (trade name) cream 2% is for use in infants, children, adolescents and adults.

IV. SCIENTIFIC DISCUSSION

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

Ketoconazole tablets

Ketoconazole tablets are indicated for treatment of infections of the skin, hair and mucosa caused by dermatophyter and/or yeasts that cannot be treated topically because of the extent of the lesion or deep infection of the skin. The SPC 4.1 text may vary across the marketed countries.

Currently the company Core Data Sheet (CCDS) for Ketoconazole tablets states that children weighing from 15-30 kg are recommended half a tablet (100 mg) once daily. Children weighing more than 30 kg are recommended the same dosage as for adults. Use of Ketoconazole tablets in children weighing less than 15 kg is not recommended.

However, in DK and other countries (Belgium) the posology section states that children weighing up to 15 kg may receive 50 mg (one forth tablet) once daily.

Ketoconazole shampoo

In the current CCDS Ketoconazole shampoo 2% is indicated for treatment and prophylaxis of infections in which Malassezia furfur (Pityrosporum) is involved including pityriasis versicolor, seborrheic dermatitis and pityriasis simplex (dandruff).

No paediatric specific indications are listed for Ketoconazole shampoo in the CCDS or SPCs across the marketed countries.

In some countries (Germany and others) the posology section (SPC 4.2) included infants, children, adolescents and adults, whereas other countries only included adults.

Ketoconazole cream

According to the current CCDS Ketoconazole cream 2% is indicated for topical treatment of dermatophyte and yeast infections (Candidiasis, pityriasis versicolor and seborrheic dermatitis). No paediatric specific indications are listed for Ketoconazole cream 2% in the CCDS or SPCs across the marketed countries.

The use of Ketoconazole cream 2% in children is mentioned in some countries SPC 4.2 section such as Germany stating that Ketoconazole cream 2% is for use in infants, children, adolescents and adults.

However, other countries have no recommendation regarding treatment of children due to lack of safety and efficacy data.

IV.2 Pharmacology

No specific pharmacodymanic studies have been conducted in children.

IV.3 Pharmacokinetics

The MAH has submitted the following pharmacokinetics information relating to oral and topical ketoconazole in the paediatric population.

Ketoconazole tablets

First author, year	Product/ Indication	Dosing	Comparator	Study type	No. of children on ketoconazole tablets/ total (age range [years])	Results
Clinical Research Report (CRR) Ketoconazole R041400/ N40190 1984[6]	Ketoconazole tablets/ Dermatophytosis	5 mg/kg single dose	Ketoconazole suspension	Open-label pharmaco-kinetic	12/12 (2-12.5)	Pharmacokinetic mean values for crushed tablets versus suspension were as follows: Time to maximum serum concentration (T_{max}): 1.3 hours versus 1.2 hours; maximum serum concentration after administration (C_{max}): 2.91±1.40 µg/mL versus 5.17±3.34 µg/mL; area under the concentration-time curve (AUC): 8.05±3.97 µg.h/mL versus 14.65±10.45 µg.h/mL; mean serum half-life (t½): 1.6 hours versus 1.5 hours, respectively. Only one patient who received the crushed tablets had peak plasma concentrations of 4 µg/mL or higher, compared with 8 of 11 (73%) children who received the suspension.

First author, year	Product/ Indication	Dosing	Comparator	Study type	No. of children on ketoconazole tablets/ total (age range [years])	Results
Bardare 1984[5]	Ketoconazole tablets/ Candidal infections	5-13 mg/kg/day, once daily 8-13 mg/kg/day, divided in 2doses	Ketoconazole suspension	Open-label pharmaco-kinetic	22/26 (<1-14);	A regimen of 5-13 mg/kg/day ketoconazole tablets achieved acceptable serum concentrations in children, provided that an antacid drug was not given at the same time. Seven patients receiving 9.61 mg/kg/day regimen divided in two doses every 12 hours showed lower peak serum concentrations (3.46 µg/mL) compared with four patients given 8.7 mg/kg once a day (6.30 µg/mL); however, between each administration, the drug concentration was less than 0.5 µg/mL for shorter periods of time with twice daily dosing (about 5 hours) compared with once daily dosing (about 11 hours). A total of 3 mg/kg/day of suspension given in three divided doses did not yield sufficiently high concentrations, which were achieved with a daily dose of 8 mg/kg or more suspension (in three doses). Large inter-patient variability in blood ketoconazole concentrations in children was observed. The authors suggested that administration twice daily of ketoconazole tablets or three times daily of suspension is preferable.

Bardare1984 [5] conducted an open-label study of ketoconazole in 26 children (16 males, 10 females; age range: 5 months to 14 years) with candidiasis. Children received oral ketoconazole (shortly before meals): ketoconazole suspension three times daily (n=9; 3-10 mg/kg) and ketoconazole tablets once (n=8; 5-13 mg/kg) or twice (n=14; 8-13 mg/kg) daily. Five patients received more than one treatment schedule. Duration of treatment ranged from 7 days to 18 months. Blood samples were collected before administration of ketoconazole and after one, two, four, six, eight, 12 and 24 hours. Serum samples were taken from the third day of treatment. Pharmacokinetic information was available in 22 of the children.

A regimen of 5-13 mg/kg/day ketoconazole tablets (in one dose or two doses) achieved acceptable serum concentrations in children and effective clinical responses, provided that an antacid drug was not given at the same time. Seven evaluable patients that were treated with ketoconazole tablets twice daily at an average daily dose of 9.61 mg/kg reached a mean maximum serum concentration after administration (C_{max}) of 3.46 µg/mL. For four evaluable patients receiving ketoconazole tablets once daily at an average daily dose of 8.70 mg/kg, mean C_{max} was 6.30 µg/mL. Among the patients treated with ketoconazole tablets, one patient showed decreased drug absorption with concomitant administration of cimetidine for gastro-oesophageal reflux and was not evaluable. Double peaks in the serum concentration were observed in two additional children given 8 mg/kg or 9.9 mg/kg of ketoconazole tablets daily. The authors suggested these may be due to enterohepatic circulation or delayed absorption. Ketoconazole was assayed in the cerebrospinal fluid of two patients. No ketoconazole levels were observed in the cerebrospinal fluid of one patient, while the serum concentration was 0.15 µg/mL; in spite of the absence of inflamed meninges in the other patient, 0.03 µg/mL of ketoconazole was detected in cerebrospinal fluid, while the serum concentration was 3.8 µg/mL. Ketoconazole suspension given 3 times daily at a dosage of 3 mg/kg/day in two patients proved to be too low to obtain both therapeutic serum concentrations and stable clinical improvement. A ketoconazole suspension dosage ranging from 4-6 mg/kg/day given to three patients yielded higher concentrations at 2 hours post-dose (0.8, 1.0, and 1.4 µg/mL), but did not completely prevent relapses. A ketoconazole suspension dose of 8 mg/kg/day or more given to 6 patients achieved acceptable serum concentrations (C_{max} 2.04 µg/mL at 2 hours post-dose and detectable concentrations at 8 hours post-dose) and definite cures.

Patients receiving ketoconazole every 12 hours showed lower C_{max} compared with patients given ketoconazole tablets once a day; however, between each administration the drug concentration was less than 0.5 µg/mL for shorter periods of time with twice daily dosing (about 5 hours) compared with once daily dosing (about 11 hours). A great interpatient variability in blood ketoconazole concentrations in children was observed. Nausea and pyrosis in four patients were the only side effects noted and no laboratory abnormalities were found. The authors suggested that twice daily administration of ketoconazole tablets or three times daily administration of suspension is preferable to achieve acceptable serum concentrations and efficacy.

CRR Ketoconazole R041400/ N40190 1984 [6] evaluated the bioavailability of ketoconazole as a suspension and as crushed tablets in a crossover study in 12 infants and children (5 males and 7 females; age range: 2-12.5 years) with diagnosed superficial dermatophytosis. No concomitant medications were permitted. Subjects received, in a fasted state, a single dose of approximately 5 mg/kg ketoconazole both as a 20 mg/mL suspension and as a ketoconazole crushed tablet mixed with 2 tablespoons of applesauce, separated by a washout period. Blood was taken before dosing, and at 0.5, 1, 2, 4 and 6 hours post-dose for plasma pharmacokinetic measurements. Liver function tests were also performed.

Mean peak plasma concentrations were observed at 1.2 and 1.3 hours after administration in patients who received the suspension and crushed tablets, respectively. The C_{max} was 2.91±1.40 µg/mL for the crushed tablets, and 5.17±3.34 µg/mL for the suspension. Only one patient who received the crushed tablets had C_{max} of 4 µg/mL or higher, compared with eight of 11 (73%) children who received the suspension. These differences were reflected in the significantly larger area under the concentration-time curve (AUC) values for patients who received the suspension (AUC=14.65±10.45 µg.h/mL) compared with those for patients who ingested tablets (AUC=8.05±3.97 µg.h/mL). Mean serum half-lives ($t_{½}$) of 1.5 hours and 1.6 hours were observed in the suspension and crushed tablet groups, respectively. Eleven patients were considered healed and one having mild residual lesions. No AEs were reported.

The authors conclude that ketoconazole was more rapidly absorbed and produced greater serum concentrations when administered in suspension to fasting infants and children rather than as crushed tablets mixed with applesauce. They also stated that both the suspension and crushed tablet produced serum concentrations of therapeutic value.

Assessor´s comments
It is noted that a pharmacokinetic study (Bandara 1984) points to twice daily administration of ketoconazole as the most optimal dose regimen. This is not compatible with the recommended posology. At the moment no recommendation can be made regarding the posology of oral ketoconazole in children.

Ketoconazole shampoo 2%

First author, year	Product/ indication	Dosing	Comparator	Study type	No. of children on ketoconazole/ total (age range [years])	Results
Van Lint 1988[7]	Ketoconazole Shampoo 2%/ dandruff/ seborrheic dermatitis	2-3 times weekly application	None	Open-label	1/33 (14)	Ketoconazole was not detectable in any of the plasma samples (detection limit, 2 ng/mL).

Van Lint 1988[7] conducted an open-label pharmacokinetics and safety study of ketoconazole shampoo 2% in 33 patients (18 males, 15 females; mean age: 39 years [range: 14-90 years]) presenting with moderate to severe seborrheic dermatitis and dandruff. Patients washed their hair with a 2% ketoconazole shampoo, twice to three times weekly. After a treatment duration of 3-26 months (mean 16 months), plasma samples and blood were taken between 2 and 24 hours after the last application of the shampoo. Plasma concentrations of ketoconazole were measured using high-performance liquid chromatography with a detection limit of 2 ng/mL. Liver function tests were also done before and during ketoconazole application.

This study included data for one 14 year old female. At the beginning of the study and during follow-up, three patients, including the 14 year old female showed abnormal liver function tests. Ketoconazole was not detectable in any of the plasma samples (detection limit, 2 ng/mL), including the adolescent female, indicating a complete absence of percutaneous absorption after chronic administration of the shampoo. No abnormalities were seen in the liver function tests during treatment. The authors concluded that the chronic use of a 2% ketoconazole shampoo in patients with seborrheic dermatitis and dandruff demonstrated no measurable Percutaneous absorption or systemic bioavailability of ketoconazole, and that the main toxicological consequence of this absence of systemic bioavailability is that the risk for systemic effects is negligible.

For information on safety, see Section 3.4.2.

Assessor's comments
Use of ketoconazole shampoo 2% in adolescents and adults is not associated with systemic absorption of the drug; however, the bioavailability of ketoconazole shampoo 2% in infancy and children has not been evaluated. For this reason and lack of clinical efficacy and safety data use of ketoconazole shampoo 2% in infants and children cannot be recommended.

Ketoconazole cream 2%

First author, year	Product/ Indication	Dosing	Comparator	Study type	No. of children on ketoconazole/ total (age range [months])	Results
Taieb 1990[8]	Ketoconazole 2% Cream/ seborrheic dermatitis	Topical application to the affected site; average 84 mg was used daily	None	Open-label	19/19 (1-11 months) Pharmacokinetics measured in 7/19 (1-5 months)	In 7 patients with extensive lesions, percutaneous absorption peaked 1-3 hours after topical treatment and was minimal. Mean plasma ketoconazole 3 hours after treatment was 64±40ng/mL. No plasma ketoconazole accumulation over the 10 day treatment was detected. An average 84 mg was used daily in all subjects (corresponding to 32±12 g of cream for 10 days of treatment).
Levron 1991.[9]	Ketoconazole 2% Cream/ seborrheic dermatitis	Topical application to the affected site; 3.1-4.9 grams used over 10 days; approximately 15 mg/kg	None	Open-label	7/7 (1-5 months)	The plasma concentrations measured by reverse phase liquid chromatography after 1-10 days of treatment were between 0.018 and 0.133 µg/mL despite the large surface affected (lower detection limit 0.005 µg/mL). The concentrations observed during the 10 days of continuous treatment in 3 infants showed that maximal absorption occurred between 1 and 3 hours after treatment. *Note: This is a subset of patients in the Taieb 1990 study.*

Taieb 1990[8] conducted an open-label study of ketoconazole cream 2% in 19 infants (11 males, 8 females; mean age: 2.8 months [range: 1-11 months]) with bipolar seborrheic rash. Clinical criteria for inclusion were: bipolar involvement of the scalp and napkin area, with secondary erythematosquamous lesions in proximal folds and on the trunk and face. For the first 5 days, infants were treated as inpatients; ketoconazole was applied once daily after bathing with white soap. At night a lubricant was used as topical treatment. Efficacy assessments were carried out before treatment and at Days 5 and 10. The quantity of drug (number of tubes) was monitored at Days 5 and 10. Plasma ketoconazole was measured by high-performance liquid chromatography (HPLC) in seven patients with extensive lesions (see Levron 1991 below for a more thorough evaluation of these patients).

Most patients had a severe bipolar seborrheic rash (mean percent surface involved: 48%) lasting from 1-9 weeks (mean 3 weeks). Percutaneous absorption peaked 1-3 hours after topical treatment and was minimal. Mean plasma ketoconazole levels 3 hours after treatment was on average 64±40 ng/mL. No plasma ketoconazole accumulation over 10 days of treatment was detected. An average 84 mg was used daily for all infants in the study (corresponding to 32±12 g of cream for 10 days of treatment).

For details of the efficacy results, see Section 3.2.3.

Levron 1991[9] conducted an open-label study of ketoconazole cream 2% in seven infants (sex not reported, mean age: 2.8 months [range: 1-5 months]), with severe bipolar seborrhoeic rash covering 50-70% of the body surface. This was a subset of patients in the Taieb 1990[8] study above. Topical ketoconazole was applied once a day on all affected areas, including those covered by diapers, for 10 days after cleansing. Plasma blood samples were drawn for pharmacokinetic analyses repeatedly 1, 3, 6, and 12 hours after application of ketoconazole on Day 1, Day 5 and Day 10. The plasma concentration of ketoconazole was determined by reverse-phase liquid chromatography.

The plasma concentrations measured in the first set of four infants were 0.133, 0.063, 0.023, and 0.040 µg/mL 3 hours after a single application of ketoconazole cream. The concentrations observed during the 10 days of continuous treatment in the three other infants in the second set measured at 1, 3, 6, and 12 hours after application, showed that maximal absorption occurred between 1 and 3 hours after treatment and ranged from 0.037-0.125 µg/mL (lower detection limit 0.005 µg/mL). The repeated applications during 10 days showed no cumulative effect of the product; the average concentrations at each point in time were not statistically different (as determined by t-test) between days 1, 5, and 10. Conditions unique to this population including age of the subjects, amount of skin surface affected, and covering with diapers may explain this absorption, which is not observed in adults. However, the author's advise caution during repeated exposure. The authors concluded that the values seen in infants were low when compared to the concentrations observed following oral administration in adults (4-9 µg/mL) and suggest the occurrence of dose-dependent systemic side effects would be highly unlikely with this approach to treatment.

Assessor's comments
After topical application of ketoconazole cream 2% in children systemic absorption is detected. One study (Taieb 1990) in infants with seborrheic dermatitis (n=19) where approximately 40 mg of Nizoral cream 2% was applied on 40% of the body surface area, plasma levels of ketoconazole were detected in 5 infants, ranging from 3-133 ng/ml.

Efficacy

The MAH has submitted the following data on children treated with oral or topical ketoconazole.

Ketoconazole tablets

First author, year	Product/ Indication	Dosing	Comparator	Study type	No. of children on ketoconazole /total (age range [years])	Results
Higashi 1984[10]	Ketoconazole tablets/ superficial mycoses	100-200 mg daily	None	Open-label	11/85 (1-18)	In all but one case, treatment was markedly effective or cured the infection; in one case, the treatment was slightly effective. No side effects were reported in children.

Higashi 1984 [10] conducted an open-label study of ketoconazole tablets in 85 patients, 11 of which were children (age range 1-18 years) with superficial mycoses. Most children were infected with *Microsporum canis* or *Trichophyton rubrum*. Daily doses ranged from 100-200 mg for duration of 14-365 days of treatment.

In all but one case in children, treatment was markedly effective (n=1) or cured (n=9) the infection; in one case, the treatment was slightly effective. No side effects were reported in children.

Assessor's comments
This study may be considered a pilot study of oral ketoconazole in children. The number of treated children is indifferent to make a recommendation regarding optimal dose regiment and duration of treatment.

Ketoconazole shampoo

3.2.2.1.1. NON-COMPARATOR STUDY

The table below summarizes a reviewed study on the efficacy of ketoconazole shampoo 2% in the treatment of seborrheic dermatitis of the scalp in adolescents and adults that lacked a comparator drug.

First author, year	Product/ Indication	Dosing	Comparator	Study type	No. of children on ketoconazole /total (age range [years])	Results
Benavides 1991[11]	Ketoconazole shampoo 2%/ seborrheic dermatitis	Topical application to the affected site for 5 minutes, 3 times/week, for 2 months	None	Open-label	5/27 (13-17)	Three females, 16-17 years of age, had an excellent response to treatment. One 16 year old male had a moderate/good response to treatment, and one 13 year old male had a poor response to treatment. No safety information is available for these subjects

Non-Comparator Study

Benavides 1991 [11] conducted an open-label study of ketoconazole shampoo 2% in 27 patients (10 males, 17 females; age range: 13-50 years) with seborrheic dermatitis of the scalp. Three females were 16-17 years of age and two males were 13 and 16 years of age. A form was prepared for each patient on which the development of the disorder; degree of involvement: mild (slight desquamation), moderate (erythema and desquamation of a regular amount), and severe (erythema and abundant desquamation) was noted, along with the presence of: pruritus, other dermatoses such as psoriasis and atopic dermatitis. All treatments were to be suspended two weeks before the use of ketoconazole 2% shampoo (Fungarest® Shampoo Janssen Pharmaceuticals). The patients were told to apply the shampoo and massage the scalp for 5 minutes, three times a week, for two months. Clinical evaluations were carried out at 2, 4 and 8 weeks to assess clinical response to the treatment as well as the patient's assessment of tolerability and efficacy.

The three females had an excellent response to treatment and one 16-year-old male had a moderate/good response to treatment. Only one 13-year-old male had a poor response to treatment. No safety information is available for these five adolescents. The authors concluded that the use of ketoconazole shampoo 2% for the control of seborrheic dermatitis of the scalp was very effective.

Assessor´s comments

Ketoconazole shampoo 2% can be used in adolescents and adults with seborrheic dermatitis. However, efficacy and safety of ketoconazole shampoo 2% has not been documented in infancy and children.

Ketoconazole cream

3.2.3.1.1. NON-COMPARATOR STUDIES

The table below summarizes a reviewed study on the efficacy of ketoconazole 2% cream in the treatment of seborrheic dermatitis in infants and toddlers that lacked a comparator drug.

First author, year	Product/ Indication	Dosing	Comparator	Study type	No. of children on ketoconazole /total (age range [years])	Results
Taieb 1990[8]	Ketoconazole 2% Cream Seborrheic dermatitis	Daily topical application to the affected site	None	Open-label	19/19 (1-11 months)	Patients were evaluated over 10 days of treatment. At day 10, 15 (78.9%) patients were almost cleared with good or excellent responses. Face and scalp lesions faded rapidly. Nonresponders corresponded to histologically psoriasiform eruptions and probable atopic dermatitis. Cutaneous tolerance to ketoconazole cream 2% was reported by physicians, nurses, and patients. *See Section 3.4.3.1.1 for the safety summary of an analysis conducted with a subgroup of 7 infants from this study (Levron 1991).*

Non-Comparator Study

Taieb 1990 [8] conducted an open-label study of ketoconazole cream 2% in 19 infants (11 males, 8 females; mean age: 2.8 months [range: 1-11 months]) with bipolar seborrheic rash. Clinical criteria for inclusion were: bipolar involvement of the scalp and napkin area, with secondary erythematosquamous lesions in proximal folds and on the trunk and face. For the first 5 days, infants were treated as inpatients; ketoconazole was applied once daily after bathing with white soap. At night a lubricant was used as topical treatment. A clinical, photographic, and microbiological assessment was carried out before treatment and at Day 5. Clinical and photographic follow-up was established on an outpatient basis at Day 10 and later if needed. A biopsy was obtained in the case of poor response at Day 5. The quantity of drug (number of tubes) was monitored at Days 5 and 10. The response to treatment was judged according to a global score taking into account the surface involved and the intensity of the dermatosis (redness, scaling, oozing): +++ = excellent; ++ = good; + = fair; +/- = poor; 0 = absent. Plasma ketoconazole was measured by HPLC in seven patients with extensive lesions.

Most patients had a severe bipolar seborrheic rash (mean percent surface involved: 48%) lasting from 1-9 weeks (mean 3 weeks). A good or excellent response was noted in 11/19 patients at Day 5. At Day 10, 15 (78.9%) patients were almost cleared with good or excellent responses. Face and scalp lesions faded rapidly. Nonresponders corresponded to histologically psoriasiform eruptions and probable atopic dermatitis. Cutaneous tolerance to ketoconazole cream 2% was reported by physicians, nurses, and patients.

For details of the pharmacokinetic results, see Section 3.1.2.3.

Assessor's comments
Ketoconazole cream 2% has been used in a limited number of children with seborrheic dermatitis. However the efficacy and safety data is insufficient for approval of ketoconazole for paediatric use.

Ketoconazole tablets

The table below summarizes a metanalysis of 133 children treated with ketoconazole for various superficial and deep mycoses.

First author, year	Product/ Indication	Dosing	Comparator	Study type	No. of children on ketoconazole/total (age range [years])	Results
CRR-Ketoconazole-R041400/49 1980a[12] (Main Report)	Ketoconazole tablets superficial and deep mycoses	2.6-27.5 mg/kg	None	Metanalysis	133/1376 (<1-14)	*Efficacy*: Tinea capitis: Remission was observed in 9 children, marked improvement in 11 children, moderate improvement in 1 child, and no response occurred in 5 children. Chronic mucocutaneous candidosis: Remission was observed in 7 children, marked improvement in 13 children, moderate improvement in 6 children, and no response was observed in 1 child. *Safety*: The incidence of adverse events (AEs) in children was unrelated to the dose of ketoconazole. AEs were mild or moderate in intensity (6 children), the most common of which was nausea/vomiting (n=3). *Note: See Section 3.4.1.1.1for pediatric appendix to the main report.*

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Metanalysis

CRR-Ketoconazole-R041400/49 1980a [12] was a statistical evaluation (metanalysis) of ketoconazole tablets in 1376 patients with various superficial and deep mycoses treated with oral ketoconazole; 133 of these patients were children (median age: 8 years [range: a few months to 14 years]; median body weight: 25 kg [range: 5-77 kg]). The most common diagnoses suffered by the children were dermatocycoses (n=34), mycoses of the hair and scalp (n=46), and chronic mucocutaneous candidosis (n=29). Few children suffered from deep mycoses (n=8). Only those patients with proven mycotic infections accompanied by clinical signs of the disease (except for cadiduria) were included in the analysis of the therapeutic effects. Patients who did not meet these criteria were evaluated for adverse events (AEs) only, as were patients who were treated with other concomitant antifungals, whose antifungal treatments started within the last month prior to ketoconazole, or were not on ketoconazole long enough to accurately assess therapeutic effects. Patients who were treated for two separate fungal infections or received two separate courses of ketoconazole were analyzed for each course or infection as separate cases. Mycological cures were assessed by culture analysis, microscopic examination, and/or serology. Clinical cures occurred when all clinical evidence of mycotic disease had disappeared. Patients were markedly improved when small residual lesions persisted without evidence of active disease, and moderately improved when the disease was still active but less so than before treatment. Adverse events were monitored and recorded.

Efficacy in children: Following doses of >3-10 mg/kg in children with tinea capitis, remission was observed in nine children, marked improvement was observed in 11 children, moderate improvement was observed in one child, and no response occurred in five children. Following doses of >4-10 mg/kg in children with chronic mucocutaneous candidosis, remission was observed in seven children, marked improvement in 13 children, moderate improvement in six children, and no response was observed in one child. In tinea capitis, the response to ketoconazole was not different with doses of 3- 5 mg/kg compared with higher doses. In chronic mucocutaneous candidosis, the response was not related to the dose.

Safety in children: The doses used in children generally exceeded 5 mg/kg (range: 3-27 mg/kg). At the time of evaluation, children had been treated for a median of 4 weeks (range: 2-54 weeks) with doses ranging from 2.6-27.5 mg/kg (median: 6.25 mg/kg). Although the doses were higher in children than those used in adults (about 3 mg/kg), there were fewer reported AEs. Six children experienced one or more AEs. The incidence of AEs in children was unrelated to the dose of ketoconazole. All AEs were slight or moderate in intensity, the most common of which was nausea/vomiting (n=3). Other AEs included: diarrhea, pruritus, dizziness, asthenia, fever and chills, headache, leucopenia and neutropenia (due to concomitant medication) and acidosis (due to underlying GI disturbance) (all n=1). A 3-year-old child (with generalized candidosis) given the highest dose of ketoconazole (27 mg/kg) did not experience any AEs; this is discussed in Section 3.4.1.1.1.

Dosage Recommendations: Based on clinical responses and an acceptable AE profile, the daily dosage recommendations by body weight in children were: ≤20 kg: 50 mg; 20-40 kg: 100 mg; >40 kg: 200 mg.

The table below summarizes the efficacy and safety information that was found related to ketoconazole tablets administration in treatment of candidal infections in the pediatric population.

First author, year	Product/ Indication	Dosing	Comparator	Study type	No. of children on ketoconazole tablets/ total (age range [years])	Results
Bardare 1984 [5]	Ketoconazole tablets/ Candidal infections	5-13 mg/kg/day, once daily 8-13 mg/kg/day, divided in 2doses	Ketoconazole suspension	Open-label, pharmaco-kinetic	22/26 (<1-14);	*Efficacy*: A regimen of 5-13 mg/kg/day ketoconazole tablets (once daily or two divided doses) achieved acceptable serum concentrations in children and effective clinical responses; however, no clinical response was evident in the patient receiving concomitant cimetidine treatment. A ketoconazole suspension regimen of 8 mg/kg/day or more (3 divided doses) achieved acceptable serum concentrations and definite cures in 6 subjects. Overall, efficacy was demonstrated by negative mycological tests (cultures or specific antibodies, or both) in 23 of 26 patients (88%), by cure in 19 patients (73%), and improvement in 3 patients (11.5%). In three patients evaluation of clinical cure/improvement was not possible due to an insufficiently proved diagnosis. *Safety*: Nausea and pyrosis in four patients were the only side effects noted and no laboratory abnormalities were found.

Assessor's comments

This is the pivotal study report including 133 children with various dermatocytoses treated with oral ketoconazole. Efficacy of ketoconazole may be questioned in dermatocytoses and mycoses of the hair and scalp. Experience in children with systemic Candidiasis is insufficient to make recommendation for dosing oral ketoconazole.

The MAH suggested dose modification (children 20-40 kg: 100 mg daily and children >40 mg: 200 mg daily) relates to this study and is different to the recommended dose regiment in CCDS (children 15-30 kg: 100 mg daily and children > 30 kg: 200 mg daily).

The treatment was fairly well-tolerated with few adverse events.

However at the moment the efficacy and safety data is insufficent to recommend the use of oral ketoconazole in children.

In addition an Article 31 Referral (EMEA/H/A-31/3114) is ongoing to assess the benefit and risks of ketoconazole containing products for oral use triggered mainly due to the potential risk of hepatotoxicity that may be higher than with other oral antimycotics.

Comparator Study

Bardare1984 [5] treated 26 children (16 males, 10 females; age range: 5 months to 14 years) with diagnosed candidiasis with different regimens of oral ketoconazole (shortly before meals): ketoconazole suspension (3-10 mg/kg) three times daily (n=9) and ketoconazole tablets once (n=8; 5-13 mg/kg) or twice (n=14; 8-13 mg/kg) daily. Five patients received more than one treatment schedule. Duration of treatment ranged from 7 days to 18 months. Before and during treatment, patients were monitored for renal function, hematologic parameters, hepatic enzymes, and serum concentrations of glucose, cholesterol, bilirubin, and alkaline phosphatase. Mycological and clinical cures were also evaluated by cultures and clinical evidence of disease.

Efficacy: A regimen of 5-13 mg/kg/day ketoconazole tablets (once daily or two divided doses) achieved acceptable serum concentrations in children and effective clinical responses; however, no clinical response was evident in the patient receiving concomitant cimetidine treatment. A ketoconazole suspension regimen of 3 mg/kg/day given in three divided doses in two patients was too low to obtain both therapeutic serum concentrations and stable clinical improvement. A ketoconazole suspension regimen ranging from 4-6 mg/kg/day (three divided doses) given to three patients yielded higher concentrations at 2 hours post-dose, but did not completely prevent relapses. A ketoconazole suspension regimen of 8 mg/kg/day or more (three divided doses) achieved acceptable serum concentrations and definite cures in six patients. Overall, the efficacy of oral ketoconazole treatment was demonstrated by negative mycological tests (cultures or specific antibodies, or both) in 23 of 26 patients (88%), by cure in 19 patients (73%), and improvement in three patients (11.5%). In three patients evaluation of clinical cure/improvement was not possible due to an insufficiently proved diagnosis.

Safety: Nausea and pyrosis in four patients were the only side effects noted and no laboratory abnormalities were found.

See Section 3.1.2.1 for further details of this study.

Assessor's comment
This study is mainly a pharmacokinetic study and assessment of the efficacy and safety of oral administration of ketoconazole in children is hampered by the low number of children receiving the ones daily ketoconazole tablet formulation.

The table below summarizes the results of an open study conducted on ketoconazole tablets for systemic candidosis.

First author, year	Product/ Indication	Dosing	Comparator	Study type	No. of children on ketoconazole/total (age range [years])	Results
CRR-Ketoconazole-R041400/37 1980[13]	Ketoconazole tablets systemic candidosis	200 mg daily (27 mg/kg)	None	Open-label	1/47 (3)	One 3-year-old child (7.5 kg body weight) was treated with 27 mg/kg ketoconazole for 56 days with no side effects. The symptoms of candidosis improved. The child, who was dystrophic at study entry, also had marked improvement in her somatic status, improved psychomotor development, and 2.5 kg weight gain during treatment. *Note: This is part of a metanalysis described in Sections 3.3.1.1.1 and 3.4.1.1.1.*

CRR-Ketoconazole-R041400/37 1980 [13] was an open-label study of ketoconazole tablets in 47 patients (10 males, 37 females; median age: 40 years [range: 3-77 years]) for the treatment of systemic candidosis. Clinical and mycological responses were evaluated following daily doses of 200-400 mg ketoconazole. One 3 year old child (7.5 kg body weight) was treated with 27 mg/kg ketoconazole (200 mg daily) for 56 days with no reported AEs. The symptoms of candidosis improved. The child, who was dystrophic at study entry, also had marked improvement in her somatic status, improved psychomotor development, and 2.5 kg weight gain during treatment. This child was also part of a statistical evaluation (metanalysis study) of children treated with oral ketoconazole as described in Sections 3.3.1.1.1 and 3.4.1.1.1.

Assessor´s comments
Based on experience in one child no dose recommendation may be made for use of oral ketoconazole in children with systemic Candidiasis.

Ketoconazole shampoo

The table below summarizes one reviewed study on ketoconazole 2% shampoo in the treatment of pityriasis versicolor in adolescents.

First author, year	Product/ Indication	Dosing	Compara-tor	Study type	No. of children on ketoconazole /total (age range [years])	Results
CRR-Ketoconazole-R041400 1999[14]	Ketoconazole Shampoo 2% pityriasis versicolor	Single application to affected area (amount not monitored)	Placebo	Randomized double-blind, placebo-controlled, multicenter, parallel-group	29/56 (12-16)	*Efficacy*: Compared with placebo, treatment with ketoconazole 2% shampoo resulted in significantly better rate of cure (p=0.032), better global evaluations (p=0.008), and greater changes from baseline for desquamation (p<0.001), erythema (p=0.027), and total symptom scores (p<0.001) at the end of the study. On Day 31, rates of cure were 11% and 41% in the placebo and ketoconazole groups, respectively. *Safety*: There was no significant difference between treatment groups in the number of subjects who experienced AEs (placebo: 37% versus ketoconazole: 38%; p=1.00). The most commonly reported AEs were influenza-like symptoms, viral infections, application site reaction, dysmenorrhea, and cough.

Comparator Studies

CRR-Ketoconazole-R041400 1999 [14] was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study of ketoconazole shampoo 2% in 56 adolescent outpatients (32 males, 24 females; median age: 14 years [range: 12-16 years]) with mycologically confirmed tinea (pityriasis) versicolor. Patients were randomly assigned to a single application of double-blind treatment with placebo shampoo (n=27) or ketoconazole 2% shampoo (n=29). Investigators made a global evaluation, performed a cellophane tape test, and assessed severity of signs and symptoms on days 10 and 31. The primary outcome measure was the rate of cure (global evaluation of healed in conjunction with a negative cellophane tape test) at 4 weeks after treatment (Day 31). Adverse events were monitored and recorded. Vital signs, physical examination and body weight were also reported.

Efficacy: Ketoconazole 2% shampoo was significantly more effective than placebo for treating tinea versicolor in adolescent subjects. Compared with placebo, treatment with ketoconazole 2% shampoo resulted in significantly better rate of cure ($p=0.032$), better global evaluations ($p=0.008$), and greater changes from baseline for desquamation ($p<0.001$), erythema ($p=0.027$), and total symptom scores ($p<0.001$) at the end of the study. On Day 31, rates of cure were 11% and 41% in the placebo and ketoconazole groups, respectively. The odds for cure for ketoconazole-treated subjects were 4.8 times higher than for placebo-treated subjects. Furthermore, subjects treated with ketoconazole 2% shampoo continued to improve throughout the 1-month evaluation period whereas improvements observed in subjects treated with placebo at Day 10 (Visit 3) were not maintained to Day 31 (Visit 4).

Safety: There was no significant difference between treatment groups in the number of subjects who experienced AEs: 21 of the 56 subjects treated (38%) experienced an AE, including 10 of 27 of the placebo-treated subjects and 11 of 29 of the ketoconazole-treated subjects (37% versus 38%; $p=1.00$). The most commonly reported AEs were influenza-like symptoms, viral infections, application site reaction, dysmenorrhea, and cough. There was 1 AE considered severe in intensity (conjunctivitis; ketoconazole-treated subject). There were no deaths or serious adverse events, and no subject discontinued the trial because of an AE.

Conclusion: The authors concluded that ketoconazole 2% shampoo, administered as a single application in adolescent subjects, was more effective than placebo for treating tinea versicolor. Ketoconazole 2% shampoo was well tolerated with an AE profile similar to that of placebo.

Assessor´s comments
Ketoconazole shampoo 2% is effective in adolescents and adults with pityriasis versicolor with an acceptable safety profile.
Ketoconazole shampoo 2% has not been used in infants and children and a dose recommendation cannot be made at present.

V. RAPPORTEUR'S PRELIMINARY CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Ketoconazole tablets 200 mg

The submitted efficacy and safety data is insufficient to make a recommendation for use of oral ketoconazole in the paediatric population.

Ketoconazole shampoo 2%

The submitted efficacy and safety data is insufficient to make a recommendation for use of ketoconazole shampoo in children, but ketoconazole shampoo may be use in adolescents.

Ketoconazole cream 2%

The submitted efficacy and safety data is insufficient to make a recommendation for use of ketoconazole cream in the paediatric population.

- **Recommendation**

Accordingly in order to harmonize the posology section of the SPC across the European contries for the various formulations of ketoconazole a Type 1B variation is to be requested from the MAH.

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

Ketoconazole tablets 200 mg

The MAH has not submitted further paediatric efficacy and safety data.

The MAH agrees with the Member States that due to the ongoing Article 31 Referral, recommendations for use of oral ketoconazole in paediatric patients is inappropriate at present.

Ketoconazole cream 2%

The MAH has not presented further paediatric efficacy and safety data.

The MAH has submitted a proposal for the pharmacokinetic properties in children.

Ketoconazole shampoo 2%

The MAH has not submitted further paediatric efficacy and safety data.

The MAH agress that ketoconazole shampoo should not be use in the paediatric population due to lack of clincal experience.

VII. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Ketoconazole tablets 200 mg

Efficacy and safety of oral ketoconazole in paediatric patients has not been documented in the submitted clinical studies. Therefore the suggested posology in children cannot be recommended.

Recommendations for use of oral ketoconazole in paediatric patients are also inappropriate at present due to the ongoing Article 31 Referral questioning the safety, i.e. hepatotocicity, of oral ketoconazole in treated patients.

Ketoconazole shampoo 2%

Due to lack of pharmacokinetics as well as efficacy and safety data use of ketoconazole shampoo 2% is not recommended in infants and children.

Ketoconazole shampoo 2% has been shown to be effective and safe in adolescents with seborrheic dermatitis and pityriasis versicolor.

Therefore the following wording in SPC 4.2 is acceptable:

SPC 4.2
Ketoconazole shampoo 2% is for use in adolescents and adults.

Ketoconazole cream 2%

The data on efficacy (n =19) and safety (n=7) of ketoconazole cream 2% is considered insufficient for approval in paediatric use.

Therefore only the following wording in SPC 4.2 is acceptable:

SPC 4.2
Ketoconazole cream is for use in adults.

The MAH has submitted supplementary pharmacokinetic data in children exposed to ketoconazole cream 2% which is found to be appropriate.

Therefore the following wording in SPC 5.2 is acceptable:

SPC 5.2
Plasma concentrations of ketoconazole were not detectable after topical administration of Nizoral 2% cream in adults on the skin. In one study in infants with seborrhoeic dermatitis

(n=19), where approximately 40 g of Nizoral 2% cream was applied daily on 40% of the body surface area, plasma levels of ketoconazole were detected in 5 infants, ranging from 32 to 133 ng/ml.

- **Recommendation**

The MAH should harmonize the SPC 4.2 and SPC 5.2 text in the European countries by initiating a Type IB procedure according to the above recommendations. Type IB variation to be requested from the MAH by 18 February 2012.