25 July 2013
EMA/CHMP/580489/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for ketoconazole containing medicinal products

Referral under Article 31 of Directive 2001/83/EC

Procedure number: EMEA/H/A-31/1314

Note

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

A review performed in 2011 by the French National Competent Authority concluded that spontaneous reports and literature data indicate that oral ketoconazole is associated with a high level of liver toxicity. The level of risk appears to be higher than that observed with other azole antifungal agents.

From 1985 to 2010, around a hundred cases of hepatic disorders with oral ketoconazole were reported to the French Pharmacovigilance Regional Centers network, including hepatitis NOS, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, hepatic failure.

In addition, a literature review retrieved more than a hundred publications related to hepatotoxicity of ketoconazole. Characteristics of acute injuries mainly included cytolysis and may lead to serious outcomes including liver transplantation. Positive rechallenge was noted in some cases. Some publications suggest that ketoconazole hepatotoxicity may be dose and/or time-dependent. In addition, based on the literature review, ketoconazole seemed to be the only antifungal agent associated with development of chronic hepatitis and cirrhosis.

In view of the above, the French Agency considered in June 2011 that the benefit-risk balance of oral ketoconazole was negative, suspended the existing marketing authorisations in France and informed the healthcare professionals and the public of its conclusions. In parallel, on 1 July 2011, France triggered a referral under Article 31of Directive 2001/83/EC. The CHMP was requested to give its opinion on whether the marketing authorisations for medicinal products containing ketoconazole for oral use, and associated names should be maintained, varied, suspended or revoked.

The procedure described in Article 32 of Directive 2001/83/EC, was applied.

2. Scientific discussion

2.1. Introduction

Ketoconazole was first registered as tablets and oral suspension in December 1980. This was followed by the registration of topical pharmaceutical forms such as cream /ointment/shampoo. Topical forms have very low systemic absorption, and are therefore not included in the present review.

In Europe, oral formulations of ketoconazole are approved in 22 Member States of the European Economic Area (EEA), after marketing authorisations have been withdrawn by the MAH in several Member States for commercial reasons. Only the 200mg tablet formulation is still available in the EEA. Ketoconazole 20mg/ml oral suspension and ketoconazole 100mg tablet formulations are no longer authorised in any EEA Member State.

Based on sales data, the post-marketing exposure for the originator product between 01 January 2005 and 30 June 2011 was estimated to be 4 855 127 person-months worldwide and 1 148 058 person-months in the European Union.

The following indications were approved within the European Union for ketoconazole-containing products, with a degree of variability in the different Member States:

Infections of the skin, hair, and mucosa, induced by dermatophytes and/or yeasts that cannot be treated topically because of the site or the extent of the lesion or deepinfection of the skin.

- *Dermatophytosis*
- *Pityriasis versicolor*
- *Malassezia folliculitis*

- *Cutaneous candidosis*
- *Chronic mucocutaneous candidosis*
- *Orapharyngeal and esophageal candidosis*
- *Chronic, recurrent vaginal candidosis*

Systemic fungal infections.

Ketoconazole does not penetrate well in the Central Nervous System. Therefore, fungal meningitis should not be treated with oral ketoconazole.

- *Paracoccidioidomycosis*
- *Histoplasmosis*
- *Coccidioidomycosis*
- *Blastomycosis*

Dosing recommendations in adults are largely consistent across Member States, at 200 mg per day which can be increased to 400 mg in cases where there is no adequate response. In children, dosing recommendations are also broadly consistent with 100 mg daily for children weighing 15-30 kg and the same dose as for adults in children weighing more than 30 kg.

Treatment duration ranges from 5 consecutive days (vaginal candidosis) to up to 6 months for systemic fungal infections such as paracoccidioidomycosis and histoplasmosis.

In 2006, the MAH of the originator product proposed amendments to the SmPC in different Member States to restrict the indication and improve the benefit-risk profile for patients receiving oral ketoconazole. These changes took into account the risk for hepatotoxicity and other adverse events, or drug interactions, as compared to the seriousness of the condition being treated. Indications representing non-life threatening conditions, especially those that required long term treatments and those for which extend efficacy data were not compelling were deleted. In addition, warnings were inserted advising the prescriber to consider use only when the potential benefits outweighed the potential risks, taking into consideration the availability of other effective antifungal.

Warnings concerning the need for monitoring of the hepatic function in all patients receiving ketoconazole tablets are included in the product information in most Member States. In Lithuania, Portugal and Spain the requirement is less strict with a need to only consider such monitoring.

2.2. Clinical safety

In order to assess the general safety of ketoconazole, relevant information from pre-clinical studies, clinical trials, post-marketing spontaneous case reports, pharmaco-epidemiological studies and published literature was assessed. Particular attention was dedicated to the issue of hepatotoxicity.

2.2.1. Mechanism of action

The mechanism of hepatotoxicity has been comprehensively discussed by the company and widely supported with literature data from 1986 to 2007. Uncertainties however still remain. From the review of the available literature, several potential mechanisms for this toxicity have been studied:

- The metabolism of ketoconazole to its primary metabolite, N-deacetyl ketoconazole (DAK), increases cytotoxicity. DAK is more cytotoxic than the parent compound, and it is believed to be largely responsible for the hepatotoxicity and the down regulation of Serum Amyloid A (SAA1 and

SAA2) and hepcidin. In vitro cytotoxicity and transcription analyses have shown that SAA and hepcidin are associated with the general toxicity of ketoconazole (Casley *et al*, 2007).

- Ketoconazole-induced hepatotoxicity is dose and time-dependent; and appears to depend, in part, upon its bio-activation by flavin-containing mono-oxygenases (FMO) to metabolites that may react with protein, and possibly, glutathione (GSH) (Rodriguez and Acosta, 1997; Rodriguez and Acosta, 2003).
- Ketoconazole-induced hepatotoxicity is related to alterations of the permeability of the rat hepatocyte membrane and the content of sulfhydryl group intracellular (Cao *et al*, 2006).
- There is a positive correlation between hepatotoxicity, lipid peroxidation injury, and DNA fragmentation induced by ketoconazole. DNA fragmentation and hepatic toxicity may be mediated by oxidative stress and accumulation of calcium (Amin and Hamza, 2005).

However Chin-Lin *et al*. (Chin-Lin Lin *et al*. Unexpected Emergence of Acute Hepatic Injury in Patients Treated Repeatedly With Ketoconazole. J Clin Gastroenterol 2008;42(4):432-3) reported dose-independent reactions and an immune-mediated mechanism. Moreover, the same authors have reported other studies on cases of hepatitis strongly suggestive of an immunoallergic response (Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006;354(7):731-9. Goodman ZD. Drug hepatotoxicity. Clin Liver Dis. 2002;6(2):381-97).

2.2.2. Non-clinical data

Ketoconazole has been tested in an battery of nonclinical safety studies including: single dose toxicity after oral (mouse, rat, Guinea-pig, dog), and i.v. (mouse, rat, Guinea-pig, dog) administration; repeat dose oral toxicity up to 12 months in the dog and 18 months in the rat, and carcinogenicity evaluations after a life-time of exposure in the mouse (18 months dosing) and rat (24-months dosing); in oral reproduction studies testing fertility and general reproduction performance in the rat, teratogenicity and embryotoxicity in mice, rats and rabbits, and perinatal/postnatal reproduction in rats. Mutagenicity was also evaluated in an extensive battery of studies.

Results reported for single and repeated dose toxicity, reproduction, mutagenicity, and carcinogenicity studies indicated the liver and endocrine system as primary target organs.

2.2.3. Clinical data

In the context of this referral procedure, the marketing authorisation holder of the originator product performed searches for any published or unpublished original-data reports presenting data, or systematic reviews of data, regarding hepatic adverse events (AEs) (as listed in Table 1) associated with the use of oral ketoconazole, or an alternative systemic antifungal agent. Results of the searches included publications of oral ketoconazole retrieved from MEDLINE, EMBASE, Derwent Drug File, SciSearch, Cited Ref Sci, and Biosis Previews, as well as unpublished internal Company reports of oral ketoconazole use (e.g., reports of clinical trials and submissions to Competent Authorities).

The output of the search was reviewed to select reports of clinical-trials, meta-analysis reviews, or of epidemiological studies, pertaining to oral ketoconazole and comparisons to other antifungal drug products, if any. In addition, company documents that had reviewed hepatic safety concerns related to oral ketoconazole, or that had supported updates to the CCDS for ketoconazole tablets were also reviewed. Periodic Safety Updated Reports (PSURs) and abstracts were excluded.

Table 1: Gastro-enterological Side Effects/Adverse Events Terms, Associated with Hepatic Adverse Events, Used in Search of "in-house" database

ALP-increased	Hepatitis	Liver-disorder
Bilirubin-decreased	Hepatobiliary-disorder	Liver-enzymes-increased
Bilirubin-direct-Increased	Hepatomegaly	Liver-function-impaired
Bilirubin-increased	Hepatorenal-syndrome	Necrosis-hepatic
Bilirubin-total-increased	Hepatotoxicity	SGGT-decreased
Bilirubinaemia	Hyperbilirubinaemia	SGGT-increased
Cholestasis	Hyperplasia-liver	SGOT-increased
Cirrhosis	Jaundice	SGPT-increased
Failure-hepatic	LDH-increased	Transaminases-increased
Hepatic-veno-occlusive-disease	Liver-damage	

ALP = alkaline phosphatase; LDH = lactate dehydrogenase; LMD = Literature Management and Documentation; SGGT = serum gamma-glutamyl transferase; SGOT = serum glutamic oxaloacetic transaminase (aspartate aminotransferase [AST]); SGPT = Serum glutamic pyruvic transaminase (alanine aminotransferase [ALT])

a. Experience of the risk of adverse drug reaction related to hepatic injury in Company-sponsored clinical trials

The safety of oral ketoconazole was evaluated in 4735 subjects in 92 clinical trials with ketoconazole tablets or suspension, that had been administered either to treat a variety of fungal infections in patient-subjects or to healthy-volunteer subjects.

The ADR terms pertaining to hepatic injury/dysfunction that are included from the analysis, with incidence are displayed in table 2.

Table 2: ADRs, with Incidences, in Hepatobiliary Disorders SOC

ADR PTs, SOC: Hepatobiliary Disorders	**Incidence (%) n=4735**
Hepatic Function Abnormal	1.18
Jaundice	0.08
Hepatitis	0.04

ADR = adverse drug reaction; PT = preferred term; SOC = system, organ, class

Based on this analysis, the point-estimate risk, in terms of the commonly-used Frequency Categories in the Summary of Product Characteristics (SmPCs), would be "Common" (≥ 1/100 to < 1/10) for any Hepatic Function Test result being abnormal, and "Rare" (≥ 1/10,000 to < 1/1,000) for Hepatitis and/or Jaundice.

b. Experience of the risk of adverse drug reaction related to hepatic injury in non-company sponsored clinical studies

Chien *et al* (1997) described a controlled cohort study of onychomycosis, 137 Taiwanese patients received long-term ketoconazole 200 mg/day; 24 patients (17.5%) had an asymptomatic transient alanine aminotransferase (ALT) elevation (2 to 10 weeks after start), which gradually normalized despite continuation of ketoconazole therapy. Four additional patients (2.9%) showed ALT elevations with clinical symptoms (28, 28, 35, and 63 days after the start of the therapy). The ALT levels of these four patients returned to normal during the seven weeks following discontinuation of therapy. None of 74 patients treated with the active comparator griseofulvin had asymptomatic increase in ALT or overt hepatitis.

c. Risk of hepatic injury in epidemiology studies

Absolute-risk estimates

The incidence of symptomatic hepatic reactions in the setting of treatment with oral ketoconazole was estimated in several epidemiology studies, in the early 1980s, to be between 1/10,000 and 1/15,000 patients.

Stricker *et al*. (1986) outlined the clinicopathological pattern of 50 'probable' and 'possible' cases of ketoconazole-associated hepatic injury and reviewed the literature. The cases had been reported during the period 1981 to April 1986 to the Netherlands Center for Monitoring of Adverse Reactions to Drugs (NARD). The pattern of clinical laboratory abnormality associated with the liver injury was hepatocellular (54%), cholestatic (16%), or mixed (25%). The authors reasoned that incidence estimates that had been reported by the earlier articles were not adequately adjusted for underreporting. Using an estimated rate of underreporting in the UK of 11 to 20% of serious and non-trivial adverse effects, they deduced an estimated incidence of symptomatic liver injury to be between 1/1000 and 1/3000 patients, “taking underreporting into consideration”.

Corbani and Burroughs (2008) reported the rate of ketoconazole symptomatic hepatotoxicity to be between 7 and 9 per 100,000.

Velayundham and Farrell (2003) estimated the frequency of ketoconazole drug-induced liver disease to be between 0.5 and 20 per 10,000 patient exposures. Frequencies of drug-induced liver disease for several other non-antifungal drugs are presented in the table 3.

Table 3: Estimated Frequency of Drug-induced Liver Disease

Drug	Frequency (exposure to drug)
Isoniazid	5 – 20/1000
Chlorpromazine	5 – 20/1000
Oestrogen	2.5/10,000
Ketoconazole	0.5 – 20/10,000
Diclofenac	1 – 5/100,000
Flucloxacillin	1/12 – 15,000
Amoxycillin-clavulanate	1.1 – 2.7/100,000

A review of the more-current literature has not yielded any new estimates of absolute risk of hepatic injury associated with oral ketoconazole other than those reported previously.

Relative-risk estimates compared with other systemic antifungal drugs

Garcia Rodriguez *et al*. (1999) conducted a retrospective cohort study from the General Practice Research Database (GPRD) in the UK among users of oral antifungal drugs. The reported background incidence of acute liver injury was estimated at 0.6 per 100,000 treatment months. Of 1,052 patients receiving ketoconazole (corresponding to 1,492 treatment months), two were diagnosed with acute liver injury (19 per 10,000 patients or 13.4 per 10,000 treatment months). For itraconazole and terbinafine, the incidences were 2/19,488 or 1/ 10,000 patients; and 1/13,430 or 0.7/10,000 patients, respectively. There were no cases of liver injury identified for the 35,833 current users of fluconazole, or for the 6,731 receiving griseofulvin. Details are provided in table 4.

Table 4: Crude Incidence Rates of Acute Liver Injury Among Current Users of Oral Antifungals

				Incidence rate (95% CI)					
				Per 10,000 patients		Per 100,000 person-months		Relative risk* (95% CI)	
Antifungal	Patients	Person-months	Cases						
Fluconazole	35,833	29,701	0	0.0	(0.0, 1.0)	0.0	(0.0, 12.9)	0.0	(0.0, 20.0)
Griseofulvin	6,731	35,841	0	0.0	(0.0, 5.5)	0.0	(0.0, 10.7)	0.0	(0.0, 16.5)
Itraconazole	19,488	19,168	2	1.0	(0.1, 3.7)	10.4	(2.9, 38.1)	17.7	(2.6, 72.6)
Ketoconazole	1,052	1,492	2	19.0	(2.3, 68.7)	134.1	(36.8, 488.0)	228.0	(33.9, 933.0)
Terbinafine	13,430	40,638	1	0.7	(0.02, 4.2)	2.5	(0.4, 13.9)	4.2	(0.2, 24.9)

CI = Confidence interval.
* Non-use person time was used as a reference group.

This study shows the higher level of risk with ketoconazole as compared to other antifungals.

Hepatobiliary events were reported in approximately 0.1% to 0.2% of patients treated with terbinafine in post-marketing surveillance studies (Hall *et al* 1997, O'Sullivan *et al* 1996). In post-marketing surveillance of more than 25,000 patients, 2 patients presented with serious hepatobiliary dysfunction (Hall *et al* 1997). The reported incidence (0.1% to 0.2%) is similar to that which was reported by Garcia Rodriguez *et al*. (1999).

Wang *et al*. (2010) reported the results of a meta-analysis of 39 randomized controlled trials of systemic antifungal agents that were published between 1989 and 2009. Ketoconazole and miconazole were not evaluated because the authors considered them to no longer be standard treatments for invasive fungal infections.

Song & Deresinski (2005) published one of the latest systematic reviews of hepatotoxicity and antifungal agents that included oral ketoconazole in the review. While this review referenced previously-published epidemiology data regarding the risk of hepatic injury associated with oral ketoconazole, it also reviewed newer information regarding other antifungal drugs, concluding that all antifungal agents had been associated with drug-induced hepatic injury. Citing the older reviews of Garcia Rodriguez, *et al*., and Como & Dismukes, this review concluded that ketoconazole appeared to be the most hepatotoxic azole antifungal agent.

d. Post-marketing spontaneous case reports

A cumulative search through 15 July 2011 for adverse events coded to the MedDRA (version 14.0) Preferred Terms (PTs) listed in the Standardised MedDRA Queries (SMQ) Hepatic disorders (broad terms) retrieved 1,512 cases, of which 1,505 cases were part of the sub-SMQ Drug related hepatic disorders (comprehensive search excluding non-drug related events such as congenital, infection, alcohol and pregnancy related events).

Non-serious cases

Of the 1,505 cases of interest; 530 (35%) were non-serious including 460 medically validated and 70 non-medically validated. 280 patients were females (53%). The mean age was 45 years. The most reported indications were onychomycosis (204/38.5%), followed by fungal infection (35/6.6%).

The daily dose, the treatment duration and time to onset data were provided in 105 cases (20%), 303 cases (57%) and 257 cases (48%), respectively. The median daily dose was 200 mg (range from 40 mg to 1200 mg). The treatment duration and time to onset, when documented, mainly ranged up to 6 months.

A total of 593 PTs of interest were reported. The most reported were hepatic function abnormal (219/37%), liver function test abnormal (163/27.5%), alanine aminotransferase increased (59/10%), aspartate aminotransferase increased (34/5.7%) hepatitis (23/3.9%), hepatic enzyme increased (21/3.5%).

Serious, non-medically validated cases

Of the 1,505 cases of interest; 95 (6%) were non-medically validated serious. The majority of the cases (58 cases/61%) were reported in female patients and the mean age was 48 years. The indication reported most often was onychomycosis (33/34.7%), followed by fungal infection (7/7.4%), tinea pedis (7/7.4%).

The daily dose, the treatment duration and time to onset data were provided in 25 cases (26%), 66 cases (69%) and 56 cases (59%), respectively. The median daily dose was 200 mg (range from 200 mg to 1200 mg). The treatment duration and time to onset, when documented, mainly ranged up to 6 months.

A total of 135 PTs of interest were reported. The most reported were hepatic function abnormal (49/36.3%), hepatitis (45/33.3%), jaundice (25/18.5%), hepatotoxicity (5/3.7%).

Serious, medically validated cases

Of the 1,505 cases of interest; 880 (58%) were medically validated serious. 558 patients were female (63.4%). The mean age was 49 years. The indication reported most often was onychomycosis (288/32.7%), followed by fungal infection (72/8.1%), candidiasis (64/7.3%), tinea pedis (37/4.2%). The daily dose, the treatment duration and time to onset data were provided in 215 cases (24%), 529 cases (60%) and 457 cases (52%), respectively. The median daily dose was 200 mg (range from 100 mg to 2400 mg). The treatment duration and time to onset, when documented, mainly ranged up to 6 months.

A hundred and eighty-six (21%) cases reported a positive dechallenge and one (0.1%) case reported a positive rechallenge.

A total of 1398 PTs of interest were reported. The most reported were hepatitis (426/30.5%), jaundice (274/19.6%), liver function test abnormal (140/10%), hepatic function abnormal (129/9.3%), liver injury (55/3.9%), hepatitis cholestatic (44/3.1%).

Fatal or life-threatening cases

Among the serious reports, 94 fatal/life-threatening cases (84 medically validated cases) were retrieved. Reported formulations were as follows: tablets in 67 (71.1%) cases, suspension in 1 (1%) case, and unspecified in 26 (27.3%) cases.

Sixteen cases were excluded since the death was not due to hepatic event (15 cases) and the symptoms were lacking (one case).

The remaining 78 cases included 64 fatal cases and 12 life-threatening cases. The majority of cases involved females (51 cases/65%) and the mean age was 52 years. The indication reported most often was onychomycosis (32/41%), followed by candidiasis (10/12.8%), fungal infection (7/9%), tinea pedis (6/7.7%).

The majority of the cases did not provide any information on the dose (55 cases/71%), duration (43/55%) and time to onset of hepatic event(s) (46/59%). Daily dose was provided in 23 cases (29%): 200 mg/day, 400 mg/day, 800 mg/day and 1200 mg/day in thirteen, seven, one and two cases, respectively. Of the 35 (45%) cases that provided treatment duration and 32 (41%) cases that provided latency information, the most common category was 1 to 6 months (22 cases and 24 cases, respectively) followed by category < one month (10 cases and 5 cases, respectively).

Of the 78 cases, nine (12%) cases presented sufficient information to determine the nature of hepatic toxicity: cholestatic (one), cytolytic (two), and mixed (six). A liver transplant was performed in nine cases.

Of the 78 cases, 19 (24%) reported laboratory tests suggesting abnormal hepatic function.

The 78 cases were further reviewed for a drug-event association and assessed for risk factors and/or possible cause(s) of hepatic events: 37 of these cases (47%) did not provide sufficient information to make such an assessment, and were excluded from further review, 23 cases (29%) presented confounding factors (eg. concomitant medications and medical history), which precluded an accurate assessment and were not further reviewed.

The remaining 18 cases did not present any confounding factors.

Seven fatal/life-threatening cases were reported with event dates after 2006 (ie, after the CCDS update that contained substantial hepatotoxicity-related revisions). Of these, one case did not present any confounding factors. In three cases, ketoconazole was indicated in onychomycosis and Cushing's syndrome and in four cases the indication was not specific (skin infection, fungal infection, suspected mycosis, unknown indication). One additional case, received after search date range, also included onychomycosis indication.

Safety overview and discussion

In order to assess the general safety of ketoconazole, relevant information from pre-clinical studies, clinical trials, post-marketing spontaneous case reports, pharmaco-epidemiological studies and published literature was assessed. Particular attention was dedicated to the issue of hepatotoxicity.

Results from non-clinical toxicity studies indicated the liver and endocrine system as primary target organs. The marketing authorisation holder extensively discussed the mechanism of hepatotoxicity, widely supported with literature data from 1986 to 2007. Several potential mechanisms for this toxicity have been identified but uncertainties still remain.

The clinical safety of oral ketoconazole was evaluated in 4735 subjects in 92 company-sponsored clinical trials of ketoconazole tablets (or suspension), administered either to treat a variety of fungal infections in patients or to healthy-volunteer subjects. Based on this analysis, the point-estimate risk, in terms of the commonly-used Frequency Categories in SmPCs, was "Common" (≥ 1/100 to < 1/10) for any Hepatic Function Test result being abnormal, and "Rare" (≥ 1/10,000 to < 1/1,000) for Hepatitis and/or Jaundice.

A cumulative search through 15 July 2011 for adverse events coded to the MedDRA (version 14.0) Preferred Terms (PTs) listed in the Standardised MedDRA Queries (SMQ) Hepatic disorders (broad terms) retrieved 1,512 cases which 1,505 cases were part of the sub-SMQ Drug related hepatic disorders (comprehensive search excluding non-drug related events such as congenital, infection, alcohol and pregnancy related events).

Of the 1,505 cases of interest; 880 (58%) were medically validated serious of which 18 life-threatening cases did not present any confounding factors and therefore are supportive of a causal role of ketoconazole. Seven fatal/life-threatening cases were reported with event dates after 2006 i.e., after the CCDS update that contained substantial hepatotoxicity-related revisions.

The incidence of symptomatic hepatic reactions in the setting of treatment with oral ketoconazole was estimated in several epidemiology studies to be between 1/10,000 and 1/15,000 patients.

The review of the literature and post-marketing data provided by the MAHs showed that

- hepatotoxicity with ketoconazole has been reported at a daily dose of 200 mg (median) which is the recommended daily dose;

- the incidence and seriousness of hepatotoxicity associated with the use of oral ketoconazole is higher than with the use of other antifungals in the treatment of superficial, sub-cutaneous and systemic fungal infections, with the highest crude incidence rate per 10 000 patients for acute liver injury among other oral antifungals and with its use associated with the development of chronic hepatitis and cirrhosis (Chien *et al*, 1997; Garcia *et al*, 1999);

- the onset of hepatotoxicity with ketoconazole usually occurs between one and six months after initiation of treatment (55% of the cases when the time to onset was documented) but has also be

reported earlier than a month (including few days) after initiation of treatment (35% of the cases when the time to onset was documented).

It was concluded that the results of the current analysis of all cases of potential hepatotoxicity with oral ketoconazole-containing medicinal product confirm the risk of serious hepatotoxicity associated with the use of oral ketoconazole, best demonstrated by the causality assessments of fatal/life-threatening hepatotoxicity cases.

2.3. Clinical efficacy

A summary of the evidence in support of the efficacy of ketoconazole is presented below, by therapeutic indication.

2.3.1. Dermatophytosis

a. Tinea corporis/cruris

Studies in this indication included over 230 evaluable patients treated with ketoconazole. These studies reported mycological, clinical or combined cure rates. Treatment with ketoconazole resulted in higher clinical or overall cure rates (ranging from 80% to 100%) than treatment with griseofulvin (ranging from 69% to 93%). Ketoconazole was more effective than griseofulvin in four of the studies summarised, although for the subgroup of patients with tinea cruris in two studies, the treatments had similar cure rates. Ketoconazole was less effective than terbinafine (clinical cure rate of 78% and 86%, respectively, but this was not statistically significant).

Results from the placebo-controlled study reported a ketoconazole cure rate of 89%.

Patients were treated for fixed periods of four weeks to 60 days or, in some studies, until cured. The clinical, mycological, and/or overall cure rates over four to six weeks ranged from 78% to 91% increasing to 98% to 100% for dosing until cured. Within the narrow date range (1982 to 1990) there was no evidence of a decline in efficacy of ketoconazole.

There were no studies that compared the efficacy of ketoconazole with that of topical comparators or with itraconazole.

b. Tinea pedis/manuum

No placebo-controlled studies were submitted for this indication.

Two randomised double-blind studies with griseofulvin as comparator included over a hundred evaluable ketoconazole-treated patients with tinea pedia or manuum. It appears from these data that ketoconazole was as effective as griseofulvin. In one of these studies, however, overall cure rates with ketoconazole and griseofulvin were comparable for tinea of the soles and palms (around 40%), but ketoconazole was not effective (0% cure rate) in the subgroup with interdigital tinea (n=4).

Results from one study showed higher cure rates for ketoconazole compared with the cure rates for griseofulvin (between 85% and 94% vs. 73% and 80%).

In three studies, the dose was not titrated up from 200 mg to 400 mg, but did allow treatment in excess of four weeks (although this was not always exceeded). At this dose and duration of treatment, ketoconazole had similar efficacy to griseofulvin and fluconazole.

In the only efficacy study comparing ketoconazole and fluconazole, ketoconazole had slightly higher mycological (92% vs. 89%) and clinical (81% vs. 68%) cure rates in the treatment of tinea pedis/manuum.

c. Tinea capitis/barbae

Ketoconazole was compared to placebo in a double-blind, randomised study of 43 children with tinea capitis, 23 of whom were initially treated with ketoconazole 200 mg per day. The median weight of patients in this study was 22 kg, so the dose for this weight was 9.1 mg/kg, which is above the 3.33 to 6.66 mg/kg recommended in the CCDS. Clinical and mycological cure rates at the end of the double-blind treatment period were both higher after ketoconazole treatment, i.e. 26% and 35%, respectively, compared to 5% and 20%, respectively, after placebo treatment. Switching non-responders to open-label ketoconazole treatment resulted in an overall cure rate of 76.5%. In this study, however, the doses in non-responders could have been doubled.

The efficacy of ketoconazole vs. griseofulvin in treating tinea capitis was assessed in 101 evaluable ketoconazole-treated patients in six studies. Most studies reported combined (i.e. mycological and clinical) cure rates. In two of these studies which included a total of 27 ketoconazole- and 32 griseofulvin-treated evaluable subjects, the reported clinical and/or overall cure rates were higher (58% and 100%) with ketoconazole than with griseofulvin (44.5% and 80%). In three other studies which included a total of 67 ketoconazole and 64 griseofulvin-treated evaluable subjects, combined cure rates were lower (20% to 74%) with ketoconazole than with griseofulvin (40% to 96%). In the remaining study that included seven ketoconazole and seven griseofulvin treated patients, cure rates were the same (57%) in both groups. The response rates for both griseofulvin and ketoconazole improved with treatment for over a month.

The dosages of ketoconazole and griseofulvin in these studies did not always comply with the current regimens recommended for this indication. Results of comparator studies should therefore be interpreted with caution.

There were no studies that compared the efficacy of oral ketoconazole with that of topical comparators, presumably because topical therapy is not efficacious in this indication.

2.3.2. Pityriasis versicolor

The efficacy of ketoconazole was assessed in 189 evaluable ketoconazole-treated patients in six placebo-controlled studies. Oral ketoconazole was shown to be efficacious in these studies with clinical and mycological cure rates (where separately reported) from 41% to 90% and from 44% to 100%, respectively, compared to a range of 8% to 17% with placebo. There were no substantial differences between five and ten days treatment duration. One of the other placebo-controlled studies reported overall cure rates after ten days of treatment in a 3-month follow-up that further demonstrated that oral ketoconazole was more effective than placebo (97.8% vs. 0%, respectively). The type of cure was not defined in the remaining study but the outcome also confirmed that oral ketoconazole was more effective than placebo (90% vs. 20%, respectively) after four weeks of treatment.

In comparative studies with fluconazole, clinical efficacy rates of 86.8% and 94.4% were noted with mycological cure rates of 73.3% and 84.7% with a standard dosing regimen. The performance of multi-dose fluconazole in these two studies diverged widely.

2.3.3. Malassezia folliculitis

In the study submitted, the Malassezia folliculitis clinical cure rate was 75% and 100% after one month of treatment with oral ketoconazole (n=20) and oral ketoconazole plus ketoconazole shampoo (n=20), respectively. In the 6-month follow-up, the cure rate (75%) was maintained without further oral treatment, but with continued topical treatments.

A non-randomised open-label controlled study in Korea achieved clinical cure in 28 of 30 patients (84%) after four weeks of treatment with ketoconazole 200 mg per day, with a similar result in a smaller topical control population. The findings from a non-comparative study showed an initial success rate of 77% after 4 weeks of treatment with oral ketoconazole, but all patients relapsed one or two months after the treatment was stopped.

2.3.4. Infections Due to Candida Species

a. Cutaneous candidosis

The efficacy of ketoconazole versus terbinafine was investigated in one of the submitted studies. Overall cure rates were 57% and 60%, respectively, and mycological cure rates were 73% and 82%, respectively, both slightly higher for terbinafine.

There were no studies that compared the efficacy of oral ketoconazole with topical comparators, itraconazole or fluconazole.

b. Chronic mucocutaneous candidosis

Two placebo-controlled studies with open-label extension phases in 24 evaluable patients on ketoconazole were submitted. Both studies showed efficacy of long-term ketoconazole treatment as compared to placebo treatment, especially for mucosal symptoms, with reported cure rates of between 83.3% and 100% on ketoconazole vs. 0% on placebo. Dermal and nail symptoms cure rates were between 16% and 50%. In one study, recurrence of symptoms in all patients necessitated a second treatment course after 36 to 48 months.

Durations of treatment were approximately six months and four months, respectively but some improvement was noted as early as two weeks.

Four non-comparative studies submitted, which included a total of more than 140 evaluable patients, showed that ketoconazole was effective; however clinical and/or mycological relapse after treatment discontinuation occurred frequently.

c. Oropharyngeal/Oesophageal candidosis

Two placebo-controlled studies and six comparative studies were submitted. The comparative studies compared ketoconazole with fluconazole (three studies), itraconazole (two studies) and clotrimazole (one study).

A total of 45 ketoconazole-treated evaluable patients with oropharyngeal candidosis were included in the two placebo-controlled studies. One study was in immune-suppressed cancer patients; the patient population in the other study was not specified. Results of both studies were statistically significant in favour of ketoconazole, with clinical cure rates of 72% to 100%, and mycological cure rates of 36% to 100%. The corresponding rates with placebo treatment were 0% to 20% and 0% to 8%, respectively.

The comparison of ketoconazole vs. fluconazole (three studies) involved 138 evaluable ketoconazole-treated patients. The results from a study in cancer patients indicated that ketoconazole was more

effective than fluconazole, with reported clinical and mycological cure rates of 89% and 66%, respectively, compared to 88% and 45%, respectively, with fluconazole treatment. Two studies in acquired immune deficiency syndrome (AIDS) patients indicated that fluconazole was more effective than ketoconazole. The clinical cure rates with ketoconazole treatment in these studies were 75% and 65%, and with fluconazole treatment 100% and 85%. Mycological cure rates with ketoconazole were 69% and 52%, respectively, and with fluconazole 87% and 91%, respectively. One of these studies was specific for oesophageal candidosis: the clinical cure rate (65% with ketoconazole and 85% with fluconazole) was well within the range of the cure rates reported in studies with purely oropharyngeal candidosis, or with combined oropharyngeal/oesophageal candidosis. Relapse rates were reported in two studies and were relatively high, with reported incidences with ketoconazole of 11% and 42% respectively, and with fluconazole 46% and 37%, respectively.

Two studies of oral ketoconazole vs. itraconazole capsules were conducted in patients with human immunodeficiency virus (HIV). Results from over 100 ketoconazole-treated patients were evaluable. Clinical cure rates with ketoconazole were slightly lower than with itraconazole (60% to 91% and 71% to 100%, respectively), but mycological cure rates were comparable (62% to 85% and 63% to 83%, respectively). Oesophageal candidosis tended to respond better to both treatments than oropharyngeal candidosis.

A comparison of ketoconazole vs. clotrimazol for treatment of oropharyngeal candidosis in immunocompromised patients (n=45) showed similar clinical (100%) and mycological (64%) cure rates with both treatments.

These studies have not defined the optimal treatment period which ranged from two to eight weeks. Longer treatment appeared necessary in oesophageal candidosis than oropharyngeal candidosis. Where documented, relapses were at a high rate and early after treatment. The numbers were too small to determine any differences between groups.

d. Vulvovaginal candidosis

There was one double-blind, randomised, placebo-controlled study submitted. The results of this study showed ketoconazole treatment to be effective, but the number of patients was relatively small (n=40). The reported clinical cure rates were 65% for the ketoconazole group and 15% for the placebo group after one week, and 80% and 25%, respectively, after four weeks.

The efficacy of oral ketoconazole vs. topical treatment was assessed in six studies. Ketoconazole was compared with clotrimazole in three studies, with fluconazole in two studies, and with miconazole in one study. A total of approximately 300 ketoconazole-treated patients were evaluable. All treatments were considered highly effective. The mycological cure rate with ketoconazole was between 60% and 96%; the mycological cure rates with topical azole antifungals were similar (from 65% to 95%). It should be noted that in four of the six studies, the cure rates reported with topical treatment were achieved after a single dose, whereas ketoconazole was always given for five days.

In two studies, the efficacy of five days of treatment with oral ketoconazole was compared with a single oral 150 mg dose of fluconazole. The results of these studies with a total of more than 120 evaluable ketoconazole-treated patients showed that ketoconazole and fluconazole treatment resulted in similar clinical (88% and 86%, respectively) and mycological (73% to 77% and 77% to 83%, respectively) cure rates.

Where analysed, initial cure rates were similar in acute and recurrent disease. Relapse or reinfection was a problem with both ketoconazole and the comparators.

2.3.5. Systemic Mycoses

a. Paracoccidioidomycosis

Ketoconazole was less effective than sulfadiazine and more effective than itraconazole in the treatment of acute or chronic paracoccidioidomycosis: the clinical cure rate achieved was 64.3% (9/14) in ketoconazole-treated patients compared with 78.6% (11/14) in sulfadiazine- and 57.1% (8/14) in itraconazole-treated patients. The duration of treatment was four to six months.

b. Histoplasmosis

A dose comparison study in 54 evaluable, non-AIDS patients showed 400 mg/day ketoconazole to be more effective than 800 mg/day. The overall response rate with the low dose was 85% for the chronic cavitary form and 72% for the disseminated form as compared to 60% and 31%, respectively, with the high dose. When only patients treated for more than 6 months were considered, the response rates were comparable for the chronic cavitary form (83% vs. 86%), but in favour of the low dose for the disseminated form (86% vs. 58%). The duration of treatment was a minimum of six months.

c. Coccidioidomycosis

A dose comparison study in 112 evaluable patients showed that 400 mg/day ketoconazole was less effective than 800 mg/day. Overall success was accomplished in 23% and 32% of the patients with the two doses, respectively. The duration of treatment was up to 15 months.

d. Blastomycosis

The ketoconazole dose-comparison study showed that a dose of 800 mg/day is more effective than 400 mg/day. The study involved 80 evaluable patients without AIDS. The combined clinical and mycological response rate with the low dose was 70% and with the high dose 85% (difference was not statistically significant). When only patients treated for more than six months were considered, the cure rate was 79% and 100%, respectively (p=0.01).

Efficacy overview and discussion

Oral ketoconazole has been approved for multiple indications across the EEA with some variation in the indications from country to country. These indications present a broad spectrum of diseases. Some diseases carry no mortality and minimal physical morbidity (e.g., pityriasis versicolor) whilst other diseases carry significant mortality and substantial morbidity (e.g., systemic fungal mycoses). The diseases range from a high incidence (e.g., chronic recurrent vaginal candidosis) to a very low incidence of diseases in the EEA that are limited to imported cases numbering in the tens rather than hundreds per annum (e.g., coccidioidomycosis).

The MAH provided a detailed report examining efficacy of oral ketoconazole by approved indication.

In general, the clinical studies submitted to support the efficacy of oral ketoconazole were limited and not conducted in line with the current guidelines. This issue has not been mitigated because ketoconazole has not been used as an active comparator for newer drugs since 2001. Efficacy studies of ketoconazole on Malassezia folliculitis, Pityriasis versicolor, Tinea Capitis and Tinea Barbae, Tinea Corporis, Tinea Cruris, Tinea Pedis, and Tinea Manuum were scarce.

There was also insufficient evidence to claim or refute a benefit for any antifungal agent in treating candidiasis and the studies presented by the MAHs on the efficacy of ketoconazole on other Candida spp. infections were limited.

Given its level of efficacy and its poor distribution in the central nervous system, the use of ketoconazole in systemic mycoses might expose patients to sub-optimal management, as translated in the therapeutic guidelines.

In general, the clinical studies submitted to support the efficacy of oral ketoconazole were outdated and not in line with the most recently agreed guidelines (Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease CHMP/EWP/1343/01 Rev. 1 Apr 2010). This issue has not been mitigated because ketoconazole has not been used as an active comparator for newer drugs since 2003.

The MAH proposed to withdraw all indications that require prolonged treatment at higher dosages, e.g., systemic mycoses requiring treatment for 6 months or longer taking into account the fact that hepatotoxicity has usually been reported after extensive cumulative exposure to ketoconazole and to limit indications to Malassezia folliculitis, Tinea capitis and chronic mucocutaneous candidiasis in patients who had either developed intolerance or failed to respond to alternative oral and/or intravenous (IV) antifungal therapy. The demonstrate the effectiveness of ketoconazole in these indications, the MAH provided a total of 40 cases, 19 cases based on clinical visits of two clinicians who kept a registry of such patients and 21 cases based on a review of the literature. All but five tinea capitis (no case of Malassezia folliculitis) corresponded to Chronic Mucocutaneous Candidiasis (n=16). Moreover, these cases were derived from old publications (from 1980 to 1986) while changes could be expected in the management of patients over more than 25 years. Of note, while ketoconazole was available since 1982, fluconazole and itraconazole became later available in the 1990's.

Overall, there was no adequate data to support a restricted indication in those cases where other options could not be used and no direct comparison with other azoles that could substantiate assumption of a potential superiority over existing azoles to expect a treatment response when others would have failed. Moreover, there are different mechanisms of resistance of fungal agents to azoles, with existing cross resistance.

2.4. Risk management plan

The following risk minimisation activities were proposed by the MAH:

- Restriction of indication with the intention to address an unmet medical need by proving prescribing physicians a treatment option in patients with malassezia folliculitis, tinea capitis or mucocutaneous candidiasis, who are either refractory or intolerant to alternative treatments
- Prescription only possible by physicians experienced in treating rare fungal skin disease and rare sub-sets of common fungal disease, reducing the number of potential prescriber to less than 20,000 in EEA compared with over 1.5 million currently;
- Limitation of the use: short treatment periods and treatment of susceptible infecting pathogens only (Candida);
- Communication on the Risk by labeling changes (enhanced liver function test (LFT) monitoring, Guidance on duration of therapy), circulation of a Direct Healthcare Professional Communication (DHPC) and regulatory communication, as well as patient reminder cards and prescriber check list cards distributed to EEA specialists experienced in treating superficial fungal infections.

The CHMP, having considered the data submitted by the MAH, was of the opinion that the proposed risk minimisation activities were not appropriate to reduce the risks to an acceptable level taking into

account the restrictions and warnings already in place. It was also considered that no restrictive use could be adequately substantiated.

2.5. Overall benefit/risk assessment

The potential for hepatotoxicity is a class effect of azole antifungals and has been long reported for ketoconazole in numerous nonclinical and clinical references.

The results of the current analysis of all cases of potential hepatotoxicity with oral ketoconazole-containing medicinal product confirmed the risk of serious hepatotoxicity associated with the use of oral ketoconazole, best demonstrated by the causality assessments of fatal/life-threatening hepatotoxicity cases.

The analysis also showed that the use of oral ketoconazole was associated with the highest crude incidence rate per 10 000 patients for acute liver injury among other oral antifungals as well as with the development of chronic hepatitis and cirrhosis.

Uncertainties still remain about ketoconazole liver toxicity mechanism. Since no additional study was provided, the hypothesis that high cumulative dose of ketoconazole is a possible risk factor for the development of serious hepatotoxicity could not be supported at this stage.

Overall, although hepatotoxicity is a class effect of azoles, the quantitative and qualitative aspects of the hepatotoxicity of ketoconazole are of particular concern.

The benefits and the risks of oral ketoconazole in dermatophytosis (Tinea Capitis, Tinea Barbae, Tinea Corporis, Tinea Cruris, Tinea Pedis, and Tinea Manuum) Pityriasis Versicolor, Malassezia folliculitis, Infections Due to Candida Species, Cutaneous candidiasis, Chronic Mucocutaneous Candidosis, Oropharyngeal Candidosis, Oesophageal Candidosis, Chronic Recurrent Vulvovaginal Candidosis, Systemic Mycoses (Paracoccidioidomycosis, Histoplasmosis, Coccidioidomycosis, Blastomycosis) were reviewed by the MAH which concluded that ketoconazole had an acceptable safety profile when used at low dose for short periods in benign diseases, but that its use at high doses for extended periods could only be supported where there was good efficacy and the risks of hepatotoxicity were outweighed by the mortality and serious morbidity of the disease.

In order to minimise the risks, the MAH has proposed to eliminate all indications that require prolonged treatment at higher dosages, e.g., systemic mycoses requiring treatment for six months or longer, taking into account that hepatotoxicity has usually been reported after extensive cumulative exposure to ketoconazole, and to limit indications to Malassezia folliculitis, Tinea capitis and chronic mucocutaneous candidiasis in patients who had either developed intolerance or failed to respond to alternative oral and/or IV antifungal therapy.

At the request of the CHMP, an Anti-Infective Scientific Advisory group (SAG) meeting was held on 3 September 2012. The experts were asked to discuss any restricted indication where the benefit/risk could be regarded as positive in the current armamentarium, and particularly the restricted indication proposed by the MAH. The experts unanimously agreed that there was no scientific evidence to support the MAH's revised indication proposal.

The SAG was of the opinion that there are no data to support the efficacy of ketoconazole when other treatments (including other azoles) have failed or resistance has been detected. Indeed, the SAG considered that the activity of the newer systemic antifungals is expected to be superior to ketoconazole. In addition, the experts would not easily foresee the utility of ketoconazole when resistance to agent(s) of the class is detected as cross resistance is frequent and there is a lack of

evidence around the potential susceptibility to ketoconazole when resistance to other azoles occurs. Moreover, tests for susceptibility to ketoconazole are not commercially available.

The SAG was also of the opinion that the pharmacokinetics / pharmacodynamics profile of ketoconazole presents similar limitations as the other systemic antifungal treatments (i.e. limited absorption, distribution) and the drug-drug interaction profile could be even worse.

The experts all concurred that ketoconazole safety profile was worse than the other systemic antifungal treatments, and there's no evidence that it would represent an option when other azoles are not tolerated. Finally, the experts unanimously agreed that these cases were anecdotal and that there was no scientific evidence available to support this claim. In addition, the use of ketoconazole in those cases would likely require a long term or repeated treatment which would be of concern for the SAG given the hepatotoxicity profile of the compound.

Although the efforts of the company to substantiate the use of ketoconazole in rescue therapy of other azoles in superficial fungal infections was acknowledged, the cases series were limited and could not adequately ascertain the benefit of the drug in rescue therapy as claimed by the company.

In addition, the claimed indications concern superficial fungal infections which are mainly confined to skin involvement (also mucous membranes for CMC), and while the social burden/inconvenience of this type of infections is not denied, the fact that they are mostly benign is also per se to be balanced with the level of hepatotoxicity of the drug.

Conclusion and recommendation

The Committee could not identify a fungal infection where the level of hepatotoxicity of the drug could be balanced by an adequately substantiated benefit and therefore concluded that the benefits of oral ketoconazole in the treatment of all antifungal indications listed above do not outweigh the risks.

Based on those conclusions, the Committee recommended the suspension of the marketing authorisations for all ketoconazole-containing products for oral use.

Divergent positions are presented in Appendix III.

2.6. Communication plan

As part of this referral procedure the CHMP agreed the wording of a Direct healthcare professional communication (DHPC) designed to inform general practitioners, dermatologists, paediatricians, infectious disease specialists, all pharmacists, including hospital pharmacists as well as relevant healthcare professional organisations, to be agreed with the National Competent Authorities (NCAs), of the suspension of the product due to the high hepatotoxicity of the product in the antifungal indications (see enclosure 12).

This communication is to be sent by 20 August 2013 to all relevant healthcare professionals.

3. Overall conclusion

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC for ketoconazole-containing products for oral use;

- The Committee reviewed all the available data on the efficacy and safety of ketoconazole-containing medicines for oral use in particular data in relation to the risk of hepatotoxicity provided by the MAHs in writing and in the oral explanations;
- The Committee considered that available data from pre-clinical studies, clinical trials, post-marketing spontaneous case reports, pharmaco-epidemiological studies and published literature have shown that the use of oral ketoconazole-containing products is associated with a high risk of serious hepatotoxicity, best demonstrated by the causality assessments of fatal/life-threatening hepatotoxicity cases;
- The Committee could not identify a fungal infection where the level of hepatotoxicity of the drug could be balanced by an adequately substantiated benefit; the Committee noted that there are currently alternatives available for the treatment of fungal infections;
- The Committee could not identify any further adequate measures to reduce the risks of ketoconazole for oral use as antifungal treatment to an acceptable level.

The Committee, as a consequence, concluded that the benefit-risk balance of ketoconazole-containing products for oral use is not favourable in the treatment of fungal infections.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the CHMP recommends the suspension of the Marketing Authorisations for all medicinal product(s) referred to in Annex I.

The conditions for the lifting of the suspension of the Marketing Authorisation(s) are set out in Annex III.

Appendix

Divergent positions

Article 31 of Directive 2001/83/EC

Procedure number: EMEA/H/A-31/1314

Ketoconazole containing medicinal products for oral use

Divergent statement

The Marketing Authorisation Holder (MAH) Janssen-Cilag wishes to retain three niche therapeutic indications for treatment of; chronic mucocutaneous candidiasis, malassezia folliculitis, tenia capitis. The conditions are rare (de facto orphan) chronic fungal skin conditions which can be deforming, debilitating, and are difficult to treat. The availability of ketoconazole, approved for these indications, represents a treatment option additional to the use of other anti-fungal agents. As in many clinical circumstances individual patients respond differently in terms of benefit and toxicity to specific treatments and perhaps the rarity of the conditions combined with divergence in the experience of clinical experts in the field accounts for the differences of expert opinion on the place of ketoconazole in the management of the conditions.

The MAH has drawn up appropriate measures to limit the use of oral ketoconazole to treatment of the three specified conditions.

In the circumstances the undersigned believe the abovementioned indications should be retained together with measures limiting and monitoring the use of the product in the target population, as discussed.

CHMP members expressing a divergent opinion:

Jens Heisterberg (DK)	25 July 2013	Signature: ……...
Alar Irs (ET)	25 July 2013	Signature: ……...
Agnes Gyurasics (HU)	25 July 2013	Signature: ……...
David Lyons (IE)	25 July 2013	Signature: ……...
Jacqueline Genoux-Hames (LU)	25 July 2013	Signature: ……...
John-Joseph Borg (MT)	25 July 2013	Signature: ……...
Piotr Fiedor (PL)	25 July 2013	Signature: ……...
Bruno Sepodes (PT)	25 July 2013	Signature: ……...
Nela Vilceanu (RO)	25 July 2013	Signature: ……...
Stanislav Primožič (SI)	25 July 2013	Signature: ……...
Sol Ruiz (co-opted)	25 July 2013	Signature: ……...
Jean-Louis Robert (co-opted)	25 July 2013	Signature: ……...

Article 31 of Directive 2001/83/EC

Procedure number: EMEA/H/A-31/1314

Ketoconazole containing medicinal products for oral use

Divergent statement

The Marketing Authorisation Holder (MAH) Janssen-Cilag wishes to retain three niche therapeutic indications for treatment of; chronic mucocutaneous candidiasis, malassezia folliculitis, tenia capitis. The conditions are rare (de facto orphan) chronic fungal skin conditions which can be deforming, debilitating, and are difficult to treat. The availability of ketoconazole, approved for these indications, represents a treatment option additional to the use of other anti-fungal agents. As in many clinical circumstances individual patients respond differently in terms of benefit and toxicity to specific treatments and perhaps the rarity of the conditions combined with divergence in the experience of clinical experts in the field accounts for the differences of expert opinion on the place of ketoconazole in the management of the conditions.

The MAH has drawn up appropriate measures to limit the use of oral ketoconazole to treatment of the three specified conditions.

In the circumstances the undersigned believe the abovementioned indications should be retained together with measures limiting and monitoring the use of the product in the target population, as discussed.

CHMP member expressing a divergent opinion:

Kolbeinn Guðmundsson (IS)	25 July 2013	Signature: …….....