Annex I

List of the names, pharmaceutical forms, strengths of the medicinal products, routes of administration, marketing authorisation holders in the member states

Member State (in EEA)	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Belgium	Janssen-Cilag NV Antwerpseweg 15-17 2340 Beerse Belgium	Nizoral 200 mg tabletten	200mg	Tablet	Oral use
Bulgaria	Jonson & Jonson D.O.O., Smartinska cesta 53, 1000 Ljubljana, Slovenia	NIZORAL	200mg	Tablet	Oral use
Cyprus	Aegis Ltd 17 Athinon street 2081 Lefkosia Cyprus	KETOZAL TABLETS 200mg	200mg	Tablet	Oral use
Cyprus	Remedica ltd Aharnon street 3508 Lemesos Cyprus	KETROZOL TABLETS 200mg	200mg	Tablet	Oral use
Cyprus	Janssen-Cilag International NV Turnhoutseweg 30 B-2340 Beers Belgium	NIZORAL TABLETS 200mg	200mg	Tablet	Oral use
Cyprus	Medochemie ltd 1-10 Constantinoupoleos street 3505 Lemesos Cyprus	TINUVIN TABLETS 200mg	200mg	Tablet	Oral use

Member State (in EEA)	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Cyprus	CDL Pharmaceutical Products ltd Agiou Spyridonos 12 7102 Larnaca Cyprus	VAFLUSON TABLETS 200MG	200mg	Tablet	Oral use
Czech Republic	Janssen-Cilag s.r.o. Karla Engliše 3201/6 15000 Praha 5 Czech Republic	NIZORAL	200mg	Tablet	Oral use
Estonia	UAB Johnson & Johnson Gelezinio Vilko g. 18A 08104 Vilnius Lithuania	NIZORAL	200mg	Tablet	Oral use
Finland	Janssen-Cilag Oy Vaisalantie 2 02130 Espoo Finland	NIZORAL	200mg	Tablet	Oral use
France	Janssen Cilag 1, rue Camille Desmoulins TSA 91003 92787 Issy-les-Moulineaux Cedex 9 France	NIZORAL 200 mg, comprimé	200mg	Tablet	Oral use
Greece	Coup ABEE Agias Barbaras 53-55 Dafni 15235 Greece	MYCOFEBRIN	200mg	Tablet	Oral use

Member State (in EEA)	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Greece	Demo ABEE 21ST Km National Highway Athens - Lamia Kryoneri 14568 Greece	AQUARIUS	200mg	Tablet	Oral use
Greece	Rafarm AEBE Korinthou 12 Neo Psychiko 15451 Greece	ILGEM	200mg	Tablet	Oral use
Greece	Angelini Pharma Hellas ABEE Achaias & Trizinias Nea Kifissia 14564 Athens Greece	SOSTATIN	200mg	Tablet	Oral use
Greece	Bros ltd Avgis & Galinis 15 Nea Kifissia Athens Greece	EBERSEPT	200mg	Tablet	Oral use
Hungary	Janssen-Cilag Kft. West Gate Business Park Tó Park 2045, Törökbálint Hungary	NIZORAL 200 mg tabletta	200mg	Tablet	Oral use
Iceland	Janssen-Cilag AB Box 7073 192 07 Sollentuna Sweden	Fungoral	200mg	Tablet	Oral use

Member State (in EEA)	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Latvia	UAB Johnson & Johnson Gelezinio Vilko g. 18A 08104 Vilnius Lithuania	Nizoral 200 mg tablets	200mg	Tablet	Oral use
Lithuania	UAB Johnson & Johnson Gelezinio Vilko g. 18A 08104 Vilnius Lithuania	Nizoral	200mg	Tablet	Oral use
Luxembourg	Janssen Cilag NV 15-17 Antwerpseweg B-2340 Beerse Belgium	Nizoral 200 mg comprimés	200mg	Tablet	Oral use
Norway	Janssen-Cilag AS Postboks 144 1325 Lysaker Norway	Fungoral	200mg	Tablet	Oral use
Poland	Polfarmex S.A. Józefów 9 99-300 Kutno Poland	Ketokonazol	200mg	Tablet	Oral use
Portugal	Janssen Farmacêutica Portugal, Lda. Estrada Consiglieri Pedroso, 69 A Queluz de Baixo 2734-503 Barcarena Portugal	Nizale	200mg	Tablet	Oral use
Romania	S.C. Arena Group S.A. Str. Ştefan Mihăileanu nr. 31 Sector 2, Bucureşti România	KETOCONAZOL ARENA 200 mg	200mg	Tablet	Oral use

Member State (in EEA)	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Romania	Terapia SA Str. Fabricii nr. 124 Cluj-Napoca Romania	NIZORAL 200 mg	200mg	Tablet	Oral use
Romania	S.C. Magistra C&C Str. Aurel Vlaicu nr. 82A 8700 Constanţa România	KETOCONAZOL 200 mg	200mg	Tablet	Oral use
Romania	S.C. Slavia Pharm S.R.L. Bd.Theodor Pallady nr. 44C Sector 3 Bucureşti România	KETOCONAZOL 200 mg	200mg	Tablet	Oral use
Romania	A.C. Helcor s.r.l. Str. Dr. Victor Babeş nr. 50 Baia Mare România	KETOSTIN 200 mg	200mg	Tablet	Oral use
Slovak Republic	Johnson & Johnson s.r.o. Karadžičova 12 821 08 Bratislava Slovak Republic	NIZORAL	200mg	Tablet	Oral use
Spain	Zeus, S.L. Collado mediano, s/n 28230 Las Rozas Madrid Spain	FUNGO ZEUS 200 mg comprimidos	200mg	Tablet	Oral use

Member State (in EEA)	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Spain	Janssen-Cilag, S.A. Pº de Las Doce Estrellas 5-7 28042 Madrid Spain	FUNGAREST comprimidos	200mg	Tablet	Oral use
Spain	Ratiopharm Espana, S.A. C/ Anabel Segura, 11 Edificio Albatros B 1ª planta 28108 Alcobendas (Madrid) Spain	Ketoconazol ratiopharm 200 mg comprimidos	200mg	Tablet	Oral use
Sweden	Janssen-Cilag AB Box 7073 192 07 Sollentuna Sweden	Fungoral®	200mg	Tablet	Oral use
The Netherlands	Janssen-Cilag B.V. Dr. Paul Janssenweg 150 5026 RH TILBURG The Netherlands	Nizoral tabletten 200 mg	200mg	Tablet	Oral use
United Kingdom	Janssen-Cilag Limited 50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG United Kingdom	Nizoral 200mg tablets	200mg	Tablet	Oral use

Annex II

Scientific conclusions and grounds for suspension of the marketing authorisations

Scientific conclusions

Overall summary of the scientific evaluation of ketoconazole-containing products for oral use (see Annex I)

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 not been considered in the present review.

In Europe, oral formulations of ketoconazole are currently approved in 20 Member States as well as in Iceland and Norway. Marketing authorisations have been withdrawn by the MAH in several Member States for commercial reasons and 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.

Within the EU, the indications approved for ketoconazole-containing products vary amongst Members States. The therapeutic indications included in the current version of the Company Core Data Sheet (CCDS) of the originator product are as follows:

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 2011, a review performed 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 antifungal agents.

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

In addition, a literature review retrieved more than 100 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. In the literature, incidence of acute injuries is variable and ranged from 1/2000 patients exposed to 12%.

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, as amended. 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 withdrawn.

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.

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 the Summary of Product Characteristics (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, 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).

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 1 and 6 months after initiation of treatment (55% of the cases when the time to onset was documented) but has also be reported earlier than 1 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.

Efficacy

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.

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 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 5 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.

Benefit –risk balance

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 the liver toxicity mechanism of ketoconazole. 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 6 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.

Amongst other risk minimisation activities proposed by the MAH were the restriction of prescribing by physicians experienced in treating rare fungal skin disease and rare sub-sets of common fungal disease, Limitation of the use: short treatment periods and treatment of susceptible infecting pathogens only (Candida) and enhanced communication on the risks.

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.

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 SAG recognised that ketoconazole could potentially be used as a last treatment option in some very rare cases. However, 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.

Taking into account all the above, the CHMP could not identify any situation that could justify exposing a patient to the level of hepatotoxicity of ketoconazole for oral use.

Overall conclusion

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.

Grounds for suspension of the marketing authorisations

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.

Annex III

Conditions for lifting the suspension of the Marketing Authorisation(s)

Conditions for lifting the suspension of the Marketing Authorisation(s)

National Competent Authorities of Member State(s) or Reference Member State(s) if applicable, shall ensure that the following conditions are fulfilled by the MAH(s):

The marketing authorisation holders should provide convincing and robust data to identify a patient population in which the clinical benefits of ketoconazole-containing products for oral use clearly outweigh the risks.