Part VI: Summary of the risk management plan

Summary of risk management plan for Ketoconazole HRA 200 mg tablets (ketoconazole)

This is a summary of the risk management plan (RMP) for Ketoconazole HRA 200 mg tablets. The RMP details important risks of Ketoconazole HRA 200 mg tablets, how these risks can be minimised, and how more information will be obtained about Ketoconazole HRA's risks and uncertainties (missing information).

Ketoconazole HRA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ketoconazole HRA should be used.

This summary of the RMP for Ketoconazole HRA 200 mg tablets should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ketoconazole HRA's RMP.

I. The medicine and what it is used for

Ketoconazole HRA 200 mg tablets is authorised for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years (see SmPC for the full indication). It contains ketoconazole as the active substance and it is given by oral route, 200 mg tablet.

Further information about the evaluation of Ketoconazole HRA's benefits can be found in Ketoconazole HRA 200 mg tablets' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/ketoconazole-hra.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Ketoconazole HRA, together with measures to minimise such risks and the proposed studies for learning more about Ketoconazole HRA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Ketoconazole HRA, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Ketoconazole HRA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Ketoconazole HRA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ketoconazole HRA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Hepatotoxicity Adrenal insufficiency QT/QTc interval prolongation/Torsade de Pointes due to interaction of ketoconazole with CYP3A4 substrates
Important potential risks	QT/QTc interval prolongation/Torsade de Pointes
Missing information	Use in paediatric population under the age of 12 years Long-term use

II.B Summary of important risks

Important identified risk **Hepatotoxicity**	
Evidence for linking the risk to the medicine	SmPC, medical and scientific literature for Ketoconazole use in the treatment of Cushing's Syndrome and as an antifungal therapy and one unpublished study in patients with Cushing's Syndrome (NIH study).
Risk factors and risk groups	Risk factors for drug-induced liver injury (DILI) include medication dose, drug lipophilicity, and extent of hepatic metabolism. Susceptibility to DILI is thought to be influenced also by concomitant hepatotoxic treatments such as paracetamol and polymedications, environmental exposures and toxins, underlying disease states or genetic predisposition. There is mixed evidence to support the role of host factors such as age, sex, and chronic liver disease in the development of DILI. A common belief held that the elderly, women and alcohol abusers are at higher overall risk of developing drug-induced hepatotoxic effects (Bell, 2009). However, a concise review

	of different causality instruments did not find any solid evidence supporting this opinion (Shapiro, 2007; Leise, 2014). In the literature, among 24 paediatric patients with Cushing's syndrome treated with ketoconazole, 02 developed serious hepatotoxicity. Therefore in adolescents, frequency of hepatotoxicity could be higher than in adults. Recent systematic review and meta-analysis of 204 eligible studies in uses other than Cushing's syndrome concluded that the incidence of ketoconazole associated hepatotoxicity was 3.6%-4.2%. The dosage and duration specific subgroup analyses did not show any significant difference among groups, while the age specific subgroup analysis showed the incidence in children and people aged >60 years was 1.4% (95% CI: 0.5%-4.2%) and 3.2% (95% CI: 1.1%-8.7%) respectively. Additionally, the incidence of the hepatotoxicity was higher in people who had oral administration of ketoconazole beyond the provisions of the usage instructions, and the incidence was 5.7% (95% CI: 4.5%-7.2%) (Yan, 2013). However, this review has some limitations due to the quality of the different publications and their heterogeneity. In most studies, the safety monitoring and the frequency of liver function monitoring were not well described, the criteria for hepatic event was not clearly defined, and only results of alanine aminotransferase (ALT) were reported. Therefore it is unknown whether some events were not captured in the studies reviewed due to lack of close follow-up, and the authors did not provide an incidence analysis based on the most reliable papers. The analysis of the dose dependency of the effect could have been impaired by the limited number of studies in which patients were treated with ketoconazole doses above 400 mg/day. Finally, in most of the studies analysed, ketoconazole was used as an antifungal agent, and the population was probably different from the population suffering from Cushing's syndrome in terms of comorbidities and may also be different in terms of frequency of follow-up visits and liver enzymes monitoring. In patients with active Cushing's syndrome, the presence of hepatic steatosis is significantly correlated with total abdominal fat area and visceral fat area (Rockall, 2003). However, the opinion on the impact of obesity and NAFLD on the development of DILI is biased and literature sources do not firmly confirm that individuals with obesity and NAFLD are systematically at increased risk for developing DILI (Andrade, 2005; Chalasani, 2008). The risk of concomitant hepatotoxic treatment and poly-medications within the group of Cushing's syndrome patients is adequately manageable and preventable as the administration of ketoconazole will be under the management and supervision of physicians experienced in endocrinology or in internal medicine. The risk of development of serious hepatic disease can be reduced to minimum by controlling liver function and liver enzymes before starting ketoconazole and by avoiding concomitant use with hepatotoxic drugs or alcohol.

	Lo Re V *et al.* (2015) described the risk of acute liver injury of oral azole antifungal medications based on epidemiological data from a large US database (patients ≥ 18 years old). In this population-based analysis, the risks of both transaminases increase (approximately above 5 ULN) and severe acute liver injury were similar among fluconazole, ketoconazole and itraconazole users. Pre-existing liver disease was identified as a strong risk factor for development of acute liver injury but it was not possible to determine if the acute liver injury was caused by the azole drug or due to the natural history of the underlying disease. Hepatotoxicity occurred mostly within the 1st month after treatment initiation, which is in line with the previous literature findings. The results from this retrospective cohort study were consistent with the Ketoconazole HRA SmPC recommendations for dosing and for liver function tests monitoring before and during therapy.
Risk minimisation measures	<u>Routine risk minimisation measures</u>: Information for healthcare professionals: • SmPC Section 4.2 - Posology and method of administration • SmPC Section 4.3 – Contraindications • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.5 - Interaction with other medicinal products and other forms of interaction • SmPC Section 4.8 – Undesirable effects • SmPC Section 5.3 - Preclinical safety data Information for patients: • Package Leaflet Section 2 - What you need to know before you take Ketoconazole HRA / Do not take Ketoconazole HRA • Package Section 2 - What you need to know before you take Ketoconazole HRA / Warnings and precautions • Package Leaflet Section 4 – Possible side effects <u>Additional risk minimisation measures</u>: • Targeted DHPC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Ketoconazole PASS (EUPAS21731) See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk **Adrenal insufficiency**	
Evidence for linking the risk to the medicine	SmPC, medical and scientific literature and one unpublished study in patients with Cushing's syndrome (the NIH study).
Risk factors and risk groups	Higher risk of adrenal insufficiency (AI) is linked to the whole group of drugs interfering with glucocorticoids synthesis or action, e.g., antifungal agents, including ketoconazole (Bornstein, 2009) and also other drugs used for Cushing's syndrome treatment (metyrapone, pasireotide and mifepristone). Acute AI usually occurs under conditions of a relative cortisol deficiency due to an increased glucocorticoid demand (e.g. in case of stress, surgery, or infection) and/or an insufficient glucocorticoid replacement (for the patients treated with a block-and-replace regimen), or in case of ketoconazole overtreatment (for the patients treated with a block only regimen). Main precipitating factors of adrenal crisis in patients at risk of AI or with a known AI are gastrointestinal and other infectious diseases. Combination of several steroidogenesis inhibitors may also result in AI. Acute AI was observed in 4/11 patients treated with a combination of ketoconazole, metyrapone and mitotane and attributed to inappropriate glucocorticoid substitution (Kamenicky, 2011).
Risk minimisation measures	<u>Routine risk minimisation measures</u>: Information for healthcare professionals: • SmPC Section 4.2 - Posology and method of administration • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.5 - Interaction with other medicinal products and other forms of interaction • SmPC Section 4.8 – Undesirable effects • SmPC Section 4.9 – Overdose Information for patients: • Package Leaflet Section 2 - What you need to know before you take Ketoconazole HRA / Warnings and precautions • Package Leaflet Section 4 – Possible side effects <u>Additional risk minimisation measures</u>: No risk minimisation measures

Important identified risk **QT/QTc interval prolongation/Torsade de Pointes due to interaction of ketoconazole with CYP3A4 substrates**	
Evidence for linking the risk to the medicine	SmPC, medical and scientific literature
Risk factors and risk groups	The risk of QTc prolongation is increased in females, patients with organic heart disease (for example congenital long QTc syndrome, myocardial infarction, congestive heart failure, dilated cardiomyopathy, hypertrophic cardiomyopathy, bradycardia), hypokalaemia and hepatic impairment (Yap, 2003). Concomitant administration of ketoconazole with certain medicinal products can increase the risk of QT prolongation. The risk of QT prolongation resulting from DDI involving ketoconazole is well-recognized and is therefore specifically addressed in the SmPC and PL. These effects have been observed for CYP3A4 substrates and is discussed within the Important identified risk of QT/QTc interval prolongation/ Torsade de Pointes (TdP) due to interaction of ketoconazole with CYP3A4 substrates (Dresser, 2000). Moreover, it is not recommended to use ketoconazole with pasireotide in patients with known problems of heart. Ketoconazole should not be co-administered with domperidone either. The results of a randomized, placebo-controlled, double-blind, double-dummy and crossover study in healthy volunteers indicated that domperidone and ketoconazole, alone and in combination, increased QTc significantly in men, and there was a positive correlation between increased QTc and concentrations of domperidone and ketoconazole in both sexes. Even though the effect of domperidone alone on QTc was small and not clinically important, concomitant use is not recommended (Boyce, 2012).
Risk minimisation measures	Routine risk minimisation measures: Information for healthcare professionals: • SmPC Section 4.3 – Contraindications • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.5 - Interaction with other medicinal products and other forms of interaction Information for patients: • Package Leaflet Section 2 - What you need to know before you take Ketoconazole HRA / Do not take Ketoconazole HRA • Package Leaflet Section 2 - What you need to know before you take Ketoconazole HRA / Warnings and precautions

	Additional risk minimisation measures: No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Ketoconazole PASS (EUPAS21731) See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk **QT/QTc interval prolongation/Torsade de Pointes**	
Evidence for linking the risk to the medicine	SmPC, medical and scientific literature
Risk factors and risk groups	The strongest risk factors for QT prolongation are persistently elevated blood pressure and left ventricular hypertrophy. Other recognized predictive factors are age, body mass, and in some studies the female gender. Women may be at higher risk probably due to a specific regulation of ionic channel expression (potassium, calcium, etc.) by sex steroids (oestrogens facilitate bradycardia-induced QT prolongation and the emergence of arrhythmia while androgens do the opposite), even though non-genomic effects may play a role as well (Drici, 2001). Male hypogonadism could also play a role in prolonging QTc interval (De Martin, 2015). In obesity, the risk increases due to electrolyte disturbances, left ventricular hypertrophy or drug effects (Frank, 1986; Pontiroli, 2004). Despite of the fact that prolonged QT interval has been observed in pre-clinical phase, the evidence of its clinical relevance is limited and additionally, clinical cases are very rare. One case of a woman with a history of coronary artery disease who developed a markedly prolonged QT interval and TdP after taking ketoconazole for treatment of fungal infection without concomitant use of other QT interval-prolonging drugs has been reported (Mok, 2005). This case indicated that even in the absence of other QT interval-prolonging drugs, precautions should be taken in ketoconazole treatment to avoid TdP, particularly for patients who have hepatic dysfunction (and thus impaired metabolism of ketoconazole), who concomitantly require CYP3A inhibitor and those who have risk factors for developing TdP. As per the SmPC, ketoconazole is contraindicated in patients with congenital or documented acquired QTc prolongation. Ruiz-Garcia et al. (2015), despite some study limitations, showed that the administration of 400 mg of ketoconazole has no significant effect on QT interval at steady-state. Moreover, in a retrospective study, De Martin et al. (2015) described the absence of untoward effect of long-term ketoconazole administration on electrocardiographic QTc interval in patients with Cushing's disease.

	Systemic complications resembling metabolic syndrome present in patients with Cushing's syndrome, increase the risk of cardiovascular complications (Arnaldi, 2003; Muiesan, 2003; Pivonello, 2005; Arnaldi, 2012). In diabetic patients, frequent among the Cushing's syndrome patients, factors potentially contributing to QT interval prolongation include insulin sensitivity and prevalent coronary artery disease (Festa, 2000).
Risk minimisation measures	<u>Routine risk minimisation measures</u>: Information for healthcare professionals: • SmPC Section 4.3 – Contraindications • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.5 - Interaction with other medicinal products and other forms of interaction • SmPC Section 5.2 – Pharmacokinetic properties • SmPC Section 5.3 - Preclinical safety data Information for patients: • Package Leaflet Section 2 - What you need to know before you take Ketoconazole HRA / Do not take Ketoconazole HRA • Package Leaflet Section 2 - What you need to know before you take Ketoconazole HRA / Warnings and precautions <u>Additional risk minimisation measures</u>: No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Ketoconazole PASS (EUPAS21731) See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information **Use in paediatric population under the age of 12 years**	
Risk minimisation measures	<u>Routine risk minimisation measures</u>: Information for healthcare professionals: • SmPC Section 4.2 - Posology and method of administration • SmPC Section 4.8 – Undesirable effects • SmPC Section 5.1 - Pharmacodynamic properties • SmPC Section 5.2 – Pharmacokinetic properties Information for patients: • Package Leaflet Section 1 - What Ketoconazole HRA is and what it is used for • Package Leaflet Section 2 - What you need to know before you take Ketoconazole HRA / Warnings and precautions <u>Additional risk minimisation measures</u>: No risk minimisation measures

Missing information **Long-term use**	
Risk minimisation measures	<u>Routine risk minimisation measures</u>: Information for healthcare professionals: • SmPC Section 4.2 - Posology and method of administration • SmPC Section 5.1 - Pharmacodynamic properties • SmPC Section 5.3 - Preclinical safety data <u>Additional risk minimisation measures</u>: Targeted DHPC

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following study is condition of the marketing authorisation:

Ketoconazole PASS (EUPAS21731): Prospective, multi-country, observational registry to collect clinical information on patients with endogenous Cushing's syndrome exposed to Ketoconazole (using the existing European Registry on Cushing's Syndrome (ERCUSYN)), to assess drug utilization pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of Ketoconazole.

Purpose of the study:

The safety profile of Ketoconazole HRA is documented and is acceptable in the context of the treatment of endogenous Cushing's syndrome, yielding to a positive benefit to risk assessment by the CHMP in September 2014.

Nevertheless, a mandatory pharmacovigilance activity has been imposed by EMA with respect to some safety concerns listed in the Risk Management Plan (RMP) and which are key to the risk-benefit assessment of Ketoconazole HRA:

- The most significant safety issue during treatment with ketoconazole is hepatotoxicity, primarily of the hepatocellular type. Fatal cases have been reported particularly when treatment is continued despite liver enzymes elevation. Due to this concern, the CHMP recommended following an article 31 referral that the marketing authorizations of oral ketoconazole-containing medicines should be suspended throughout the European Union (EU) (26 July 2013, EMA/458028/2013). Following Ketoconazole HRA approval for the treatment of endogenous Cushing's syndrome, hepatotoxicity remains a concern that needs to be followed up post approval and the CHMP requested HRA Pharma to collect post approval data through a registry and annually submit results for review. The risk is considered manageable when the Summary of Product Characteristics (SmPC) recommendations are followed and contraindications are respected; concurrent use of other potential hepatotoxic drugs is avoided and with an adequate monitoring of liver function tests prior, during treatment and regularly in case of increase of dose. The possibility of a higher rate of hepatotoxicity in adolescents is an additional safety issue that deserves to be mentioned. Strict criteria for stopping the treatment in case of increase in liver enzymes ≥ 3 fold the ULN are also clearly indicated to the prescriber and the patient.
- The risk of QT/QTc prolongation/ torsades de pointes with ketoconazole is low and has mainly been shown with concomitant use of QT interval prolonging drugs which should therefore be avoided as indicated in the SmPC. ECG monitoring before and on Ketoconazole HRA is recommended in all patients to check for QT/QTc interval.

As part of this Post-Authorisation Measure (PAM) (EMEA/H/C/003906/ANX002), as committed, the MAH submitted the results of the ERCUSYN feasibility evaluation on 19 February 2015. Following the receipt of the positive updated assessment's report in September 2015, the HRA Pharma submitted the PASS protocol version 3.0 in December 2015. The final study protocol for this observational PASS has been approved by PRAC on 01 September 2017 (endorsing version 8.0 of the protocol).

The primary objective is to collect clinical information on patients with endogenous Cushing's syndrome exposed to Ketoconazole HRA and assess Ketoconazole HRA safety with a particular focus on the safety concerns of hepatotoxicity and QT prolongation with Ketoconazole HRA only and in interaction with CYP3A4 substrates.

The secondary objectives are to collect and assess other safety data, to evaluate the effectiveness and drug utilization patterns of Ketoconazole HRA.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Ketoconazole HRA 200 mg Tablets.