

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ketoconazole HRA 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg ketoconazole.

Excipient with known effect: each tablet contains 19 mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Off-white to light cream, round, 10 mm diameter, biconvex.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ketoconazole HRA is indicated for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.

4.2 Posology and method of administration

Treatment should be initiated and supervised by physicians experienced in endocrinology or internal medicine and having the appropriate facilities for monitoring of biochemical responses since the dose must be adjusted to meet the patient's therapeutic need, based on the normalisation of cortisol levels.

Posology

Initiation

The recommended dose at initiation in adults and adolescents is 400-600 mg/day taken orally in two or three divided doses and this dose can be increased rapidly to 800-1200 mg/day in two or three divided doses.

At treatment initiation, 24-hour urinary free cortisol should be controlled every few days/weeks.

Adjustment of the posology

Ketoconazole HRA daily dose should be periodically adjusted on an individual basis with the aim to normalise urinary free cortisol and/or plasma cortisol levels.

- A dose increase of 200 mg/day every 7 to 28 days may be considered if urinary free cortisol and/or plasma cortisol levels are above the normal range, as long as the dose is tolerated by the patient;

- A maintenance dose from 400 mg/day to a maximal dose of 1200 mg/day taken orally in 2 to 3 divided doses may be required to restore normal cortisol levels. In most of the publications the maintenance dose varied between 600 mg/day and 800 mg/day;
- When the effective dose of Ketoconazole HRA is established, monitoring of urinary free cortisol and/or plasma cortisol levels may be performed every 3 to 6 months (see section 4.4);
- In the case of adrenal insufficiency and depending on the severity of the event, the dose of Ketoconazole HRA should be decreased by at least 200 mg/day or the treatment should be temporarily discontinued and/or a corticosteroid therapy should be added until the resolution of the event. Ketoconazole HRA can be reintroduced thereafter at a lower dose (see section 4.4);
- Treatment with Ketoconazole HRA can be stopped abruptly without a need for progressive dose decrease where a change in the therapeutic strategy (eg surgery) is desired.

Monitoring of liver function

Before starting the treatment, it is mandatory:

- to measure liver enzymes (ASAT, ALAT, gammaGT and alkaline phosphatase) and bilirubin
- to inform the patients about the risk of hepatotoxicity, including to stop the treatment and to contact their doctor immediately if they feel unwell or in the event of symptoms such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine. If these occur, treatment should be stopped immediately and liver function tests should be performed.

Due to the known hepatotoxicity of ketoconazole, the treatment must not be initiated in patients with liver enzymes levels above 2 times the upper limit of normal (see section 4.3).

During the treatment:

- close clinical follow-up should be undertaken
- measurement of liver enzymes (ASAT, ALAT, gamma GT and alkaline phosphatase) and bilirubin, should be performed at frequent intervals:
 - o weekly for one month after initiation of the treatment
 - o then monthly for 6 months
 - o weekly during one month whenever the dose was increased.

In the case of an increase in liver enzymes of less than 3 times the upper limit of normal, more frequent monitoring of liver function tests should be performed and the daily dose should be decreased by at least 200 mg.

In the case of an increase in liver enzymes equal to or greater than 3 times the upper limit of normal, Ketoconazole HRA should be stopped immediately and should not be reintroduced due to the risk of serious hepatic toxicity. Ketoconazole HRA should be discontinued without any delay if clinical symptoms of hepatitis develop.

In case of long term treatment (more than 6 months):

Although hepatotoxicity is usually observed at treatment initiation and within the first six months of treatment, monitoring of liver enzymes should be done under medical criteria. As a precautionary measure, in case of a dose increase after the first six months of treatment, monitoring of liver enzymes should be repeated on a weekly basis for one month.

Dosing regimens for maintenance therapy

Subsequent maintenance therapy can be administered in one of two ways:

- Block-only regimen: the maintenance dose of Ketoconazole HRA may be continued as described above;
- Block-and-replace regimen: the maintenance dose of Ketoconazole HRA should be further increased by 200 mg and concomitant corticosteroid replacement therapy should be added (see section 4.4).

Special populations

Paediatric population

The safety and efficacy of Ketoconazole HRA in children aged less than 12 years have not been established. No recommendation on posology can be made for children under 12. The posology in adolescents above the age of 12 years is the same as in adults (see section 5.1 and 5.2).

Elderly patients

Data on the use of Ketoconazole HRA in patients older than 65 years are limited, but there is no evidence to suggest that specific dose adjustment is required in these patients (see section 5.2).

Patients with renal impairment

Although data are limited, the pharmacokinetics of Ketoconazole HRA are not significantly different in patients with renal failure compared to healthy subjects, and no specific dose adjustment is recommended in this population.

Patients with hepatic impairment

Ketoconazole is contraindicated in patients with acute or chronic hepatic impairment (see sections 4.3, 4.4 and 5.3).

Gender, weight and race

No formal evaluation has been conducted to investigate the potential differences in ketoconazole pharmacokinetics between males and females and data evaluating the effect of weight on pharmacokinetics of ketoconazole are very limited.

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to ketoconazole and/or to any imidazole antifungal medication, or to any of the excipients listed in section 6.1
- Acute or chronic liver disease and/or if pre-treatment liver enzymes levels are above 2 times the upper limit of normal (see sections 4.2 and 4.4)
- Pregnant women (see section 4.6)
- Breastfeeding women (see section 4.6)
- Congenital or documented acquired QTc prolongation
- Concomitant therapy with any of the following medicinal products which may interact and result in potentially life-threatening adverse reactions (sections 4.4 and 4.5):
 - o CYP3A4 metabolised HMG-CoA reductase inhibitors (eg simvastatin, atorvastatin and lovastatin) due to an increased risk of skeletal muscle toxicity including rhabdomyolysis
 - o eplerenone due to an increased risk of hyperkalemia and hypotension
 - o substances that may have their plasma concentrations increased and have QT prolonging potential : methadone, disopyramide, quinidine, dronedarone, pimozide, sertindole, saquinavir (saquinavir/ritonavir 1000/100 mg bid), ranolazine, mizolastine, halofantrine
 - o dabigatran due to an increased bleeding risk
 - o triazolam, oral midazolam and alprazolam due to potential for prolonged or increased sedation and respiratory depression

- ergot alkaloids (eg dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) due to an increased risk of ergotism and other serious vasospastic adverse events
- lurasidone
- quetiapine due to an increased risk of toxicity
- telithromycin and clarithromycin in patients with severe renal impairment due to an increased risk of hepatotoxicity and QT interval prolongation
- felodipine, nisoldipine due to an increased risk of oedema and congestive heart failure
- colchicine in patients with renal impairment due to an increased risk of severe adverse reactions
- irinotecan due to an alteration of the metabolism of this medicinal product
- everolimus, sirolimus (also known as rapamycin) due to an increase of the plasma concentrations of these medicinal products
- vardenafil in men older than 75-years due to increased risk of adverse events
- fesoterodine and solifenacin in patients with renal impairment

The list above is not an inclusive list of compounds that may interact with ketoconazole and result in potentially life-threatening reactions.

4.4 Special warnings and precautions for use

Monitoring of liver function

Liver enzymes should be monitored in all patients receiving Ketoconazole HRA. Due to the risk of serious hepatic toxicity, close follow-up of patients is required (see section 4.2).

Monitoring of adrenal function

Adrenal function should be monitored at regular intervals since adrenal insufficiency can occur during the treatment under conditions of a relative cortisol deficiency due to an increased glucocorticoid demand (e.g. in case of stress, surgery, or infection); and/or in case of Ketoconazole HRA overtreatment (for the patients treated with a block-only regimen); or if there is insufficient glucocorticoid replacement therapy (for the patients treated with a block-and-replace regimen). Serum or plasma and/or salivary cortisol and/or urinary free cortisol levels should be monitored, within one week following Ketoconazole HRA initiation as a minimum, and then periodically thereafter. When urinary free/serum/ plasma cortisol levels are normalised or close to target and the effective dose of Ketoconazole HRA is established, monitoring can be undertaken every 3 to 6 months (see section 4.2 for dose adjustment in case of adrenal insufficiency).

All patients should be monitored and informed about the signs and symptoms associated with hypocortisolism (e.g. weakness, fatigue, anorexia, nausea, vomiting, weight-loss, hypotension, hyponatraemia, hyperkalaemia and/or hypoglycaemia).

If clinical symptoms are suggestive of adrenal insufficiency, cortisol levels should be measured and Ketoconazole HRA should be temporarily discontinued or the dose reduced and if necessary corticosteroid substitution should be initiated. Ketoconazole HRA can be resumed thereafter at a lower dose (see section 4.2).

Block and replace regimen

Patients treated with a block-and-replace regimen should be taught to adjust their glucocorticoid replacement therapy dose under conditions of stress (see section 4.2). In addition, they should receive an emergency card and be equipped with an emergency glucocorticoid set.

Monitoring of the QTc interval

Monitoring for an effect on the QTc interval is advisable. An ECG should be performed:

- Prior to the start of Ketoconazole HRA

- Within one week after the beginning of the treatment
- As clinically indicated thereafter.

In case of co-administration of an agent known to increase QTc interval (see section 4.5), ECG monitoring is recommended.

Contraception

Women must be provided with comprehensive information on pregnancy prevention. As a minimum requirement, women of childbearing potential must use an effective method of contraception (see section 4.6).

Decreased gastric acidity

Absorption is impaired when gastric acidity is decreased. Acid-neutralising medicines (e.g. aluminium hydroxide) should not be administered for at least 2 hours after the intake of Ketoconazole HRA. In patients with achlorhydria, such as certain AIDS patients and patients on acid secretion suppressors (e.g. H₂-antagonists, proton pump inhibitors), it is advised to administer Ketoconazole HRA with an acidic beverage eg cola beverage, orange juice.

If acid secretion suppressors are added to or removed from the concomitant medication then ketoconazole dose should be adjusted according to cortisol levels.

Potential interaction with medicinal products

Ketoconazole HRA has a high potential for clinically important medicinal products interactions.

Ketoconazole HRA is mainly metabolised through CYP3A4. Co-administration of potent enzyme inducers of CYP3A4 may decrease the bioavailability of Ketoconazole HRA. A review of concomitant medicinal products should be conducted when initiating ketoconazole treatment since ketoconazole is a known strong CYP3A4 inhibitor. The SmPC for concomitantly used products must be consulted for the recommendations regarding co-administration with strong CYP3A4 inhibitors.

Ketoconazole HRA is a potent inhibitor of CYP3A4: inhibition of CYP3A4 by Ketoconazole HRA can increase patients' exposure to a number of medicinal products which are metabolised through this enzymatic system (see section 4.5).

Ketoconazole HRA is also a potent inhibitor of P-gp: inhibition of P-gp by Ketoconazole HRA can increase patients' exposure to medicinal products which are P-gp substrates (see section 4.5).

CYP3A4-metabolised and/or P-gp substrates known to prolong the QT interval may be contraindicated with Ketoconazole HRA, since the combination may lead to an increased risk of ventricular tachyarrhythmias, including occurrences of torsade de pointes, a potentially fatal arrhythmia (see section 4.3).

Use with hepatotoxic medicinal products

Co-administration of Ketoconazole HRA and other medications known to have potentially hepatotoxic effect (eg paracetamol) is not recommended since the combination may lead to increased risk of liver damage.

Use with Pasireotide

Co-administration of Ketoconazole HRA and pasireotide is not recommended since the combination can lead to QT prolongation in patients with known cardiac rhythm disorders (see section 4.5).

Coexisting inflammatory/autoimmune disorders

Exacerbation or development of inflammatory/autoimmune disorders has been described after Cushing's syndrome remission, including after treatment with ketoconazole. Patients with Cushing's syndrome and coexisting inflammatory/autoimmune disorders should be supervised after normalisation of cortisol levels on ketoconazole.

Alcohol

Patients should be advised against alcohol consumption while on treatment (see section 4.5).

Warning regarding excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactase intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

See section 4.3 Contraindications for the list of the medicinal products that are contraindicated during treatment with Ketoconazole HRA.

Medicinal products affecting the absorption of Ketoconazole HRA

Medicinal drugs affecting gastric acidity impair the absorption of Ketoconazole HRA (see section 4.4).

Effects of other medicinal products on the metabolism of Ketoconazole HRA

Ketoconazole HRA is mainly metabolised by cytochrome CYP3A4.

Enzyme-inducing drugs such as rifampicin, rifabutin, carbamazepine, isoniazid, nevirapine, mitotane and phenytoin may significantly reduce the bioavailability of Ketoconazole HRA. Use of Ketoconazole HRA with potent enzyme inducers is not recommended.

Potent inhibitors of CYP3A4 (e.g. antivirals such as ritonavir, ritonavir-boosted darunavir and ritonavir-boosted fosamprenavir) may increase the bioavailability of Ketoconazole HRA, these drugs should be used with caution when co-administered with Ketoconazole HRA and patients should be monitored closely for signs and symptoms of adrenal insufficiency. Ketoconazole HRA dose should be adjusted accordingly.

Effects of Ketoconazole HRA on the metabolism of the other medicinal products

- Ketoconazole HRA is a potent inhibitor of CYP3A4 and can inhibit the metabolism of drugs metabolised by this enzyme. This can result in an increase and/or prolongation of their effects, including adverse effects.
- Ketoconazole HRA can inhibit the transport of drugs by P-gp, which may result in an increased plasma concentration of these drugs.
- Ketoconazole inhibits BCRP (Breast Cancer Resistance Protein) in *in vitro* studies. Data of inhibition indicate that there is no risk of interaction with BCRP substrates at the systemic level. However ketoconazole may be an inhibitor of BCRP at the intestinal level at clinically relevant concentrations. Considering the rapid absorption of ketoconazole, intake of BCRP substrates should be postponed for 2 hours after ketoconazole intake.

Table 1 Interactions and recommendations for co-administration.

Interactions between ketoconazole and other medicinal products are listed in the table below (increase is indicated as “↑”, decrease as “↓”, an no change as “↔”). The degrees of interaction mentioned below are not absolute values and may be dependent on the ketoconazole dose given i.e. many results are reported following a ketoconazole dose of 200 mg and a stronger interaction may be expected at a higher dose and/or shorter dosing interval. The following list is not an inclusive list of interactions between ketoconazole and other drugs

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
<i>Analgesic opioid</i>		
Methadone	Potential ↑ in plasma concentrations of methadone	Contraindicated due to the increased risk of serious cardiovascular events including QT prolongation and torsade de pointes, or respiratory or CNS depression (see section 4.3).
Buprenorphine IV and sublingual	Buprenorphine: AUC: ↑ 1.5-fold Cmax: ↑1.7-fold	Careful monitoring. The buprenorphine dose should be adjusted.
Alfentanil, fentanyl	Potential ↑ in plasma concentrations of alfentanil and fentanyl	Careful monitoring of adverse effects (respiratory depression, sedation) is recommended. It may be necessary to lower the dose of alfentanil and

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
		fentanyl.
Oxycodone	↑in plasma concentrations of oxycodone have been observed	Careful monitoring. The oxycodone dose may be adjusted.
<i>Antiarrhythmics</i>		
Disopyramide Quinidine	Potential ↑in plasma concentrations of disopyramide and quinidine	Contraindicated due to the risk of serious cardiovascular events including QT prolongation (see section 4.3).
Dronedarone	Repeated doses of 200 mg ketoconazole daily resulted in a 17-fold increase in dronedarone exposure	
Digoxin	Potential ↑in plasma concentrations of digoxine	Careful monitoring of digoxin levels is recommended.
<i>Anticoagulants and antiplatelet drugs</i>		
Rivaroxaban	Rivaroxaban: AUC: ↑ 2.6-fold Cmax: ↑1.7-fold	Not recommended due to an increased bleeding risk.
Cilostazol	Cilostazol: AUC: ↑ 2.2 fold The overall pharmacological activity of cilostazol increases 35% when co-administered with ketoconazole.	Careful monitoring A cilostazol dosage of 50 mg twice daily is recommended in combination with Ketoconazole HRA.
Warfarin and other coumarin-like drugs	Potential ↑in plasma concentrations of warfarin	Careful monitoring INR (international normalised ratio) monitoring recommended.
Dabigatran	Dabigatran: AUC: ↑ 2.6-fold Cmax: ↑2.5-fold	Contraindicated due to an increased bleeding risk (see section 4.3).
<i>Anticonvulsants</i>		
Carbamazepine Phenytoin	Potential ↑in plasma concentrations of carbamazepine and phenytoin Potential ↓ in plasma concentrations of ketoconazole are expected. (CYP3A enzyme induction)	Not recommended. (See also “Effects of other medicinal products on the metabolism of Ketoconazole HRA ”).
<i>Antidiabetics</i>		
Repaglinide	Repaglinide: AUC: ↑ 1.2-fold Cmax: ↑ 1.2-fold	Careful monitoring. Dose adjustment of repaglinide may be required.
Saxagliptin	Saxagliptin: AUC: ↑ 2.5-fold Cmax: ↑ 1.6-fold Associated with a decrease in corresponding values for the active metabolite	Careful monitoring. Dose adjustment of saxagliptin may be required.
<i>Anti-infectives</i>		
Rifabutin Rifampicin Isoniazid	Potential ↑ in plasma concentrations of rifabutine. Potencial ↓ in plasma concentrations of ketoconazole are expected. (CYP3A4 enzyme induction)	Not recommended. (See also “Effects of other medicinal products on the metabolism of Ketoconazole HRA ”)
Telithromycin	Telithromycine:	Not recommended.

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
Clarithromycin	AUC: ↑ 2-fold Cmax: ↑1.5-fold Potential ↑in plasma concentrations of clarithromycin	Contraindicated in patients with severe renal impairment due to the risk of QT interval prolongation and serious hepatic adverse reactions (see section 4.3).
Praziquantel	↑in plasma concentrations of praziquantel have been observed	Careful monitoring. Dose adjustment of praziquantel may be required.
<i>Antimigraine Drugs</i>		
Ergots alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)	Potential ↑in plasma concentrations of ergot alkaloids	Contraindicated due to the increased risk of ergotism and other serious vasospastic adverse events (see section 4.3).
Eletriptan	Eletriptan: AUC: ↑ 5.9-fold Cmax: ↑ 2.7-fold	Not recommended.
<i>Antineoplastics</i>		
Sunitinib Dasatinib Lapatinib Nilotinib Erlotinib	Sunitinib AUC: ↑ 1.5-fold Cmax: ↑ 1.5-fold Lapatinib: AUC: ↑ 3.6-fold Nilotinib: AUC: ↑ 3.0-fold Erlotinib: AUC: ↑ 1.9-fold Cmax: ↑ 1.7-fold Dasatinib ↑in plasma concentrations of Dasatinib have been observed	Not recommended due to the risk of increased exposure to these drugs and QT prolongation.
Irinotecan	Irinotecan: AUC: ↑ 2.1-fold	Contraindicated due to an alteration of the metabolism of this medicinal product (see section 4.3).
Bortezomib Busulfan Docetaxel Imatinib	Bortezomib: AUC: ↑ 1.4-fold Imatinib: AUC: ↑ 1.4-fold Cmax: ↑ 1.3-fold ↑in plasma concentrations of docetaxel have been observed Potential ↑in plasma concentrations of busulfan	Careful monitoring. Dose adjustment of each drug may be required.
Paclitaxel	Paclitaxel: No change in plasma concentration were shown with paclitaxel concentrate. No studies were performed with albumin bound nanoparticles.	Careful monitoring. Dose adjustment of paclitaxel may be required.
Vincristine, vinblastine (vinca alkaloids)	Potential ↑in plasma concentrations of vinca alkaloids-	Careful monitoring as it may cause an earlier onset and/or an increased severity of side-effects.
<i>Antipsychotics, Anxiolytics and</i>		

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
<i>Hypnotics</i>		
Triazolam Alprazolam Midazolam oral	AUC: ↑ have been observed Cmax: ↑ have been observed	Contraindicated due to the risk of potentially prolonged or increased sedation and respiratory depression (see section 4.3).
Midazolam IV	Midazolam: AUC: ↑ 1.6-fold	Careful monitoring. Dose adjustment of midazolam IV may be required.
Lurasidone	Lurasidone: AUC: ↑ 9-fold Cmax: ↑ 6-fold	Contraindicated due to the increased risk of adverse events (see section 4.3).
Pimozide	Potential ↑ in plasma concentrations of pimozide.	Contraindicated due to the risk of serious cardiovascular events including QT prolongation (see section 4.3).
Buspirone	Potential ↑ in plasma concentrations of buspirone.	Careful monitoring. Dose adjustment of buspirone may be required.
Aripiprazole	Aripiprazole AUC: ↑ 1.6-fold Cmax: ↑ 1.4-fold	Careful monitoring. Aripiprazole dose should be reduced to approximately one-half of its prescribed dose.
Haloperidol	Potential ↑ in plasma concentrations of haloperidol.	Not recommended due to the increased risk of QT prolongation and extrapyramidal symptoms. It may be necessary to reduce haloperidol dosage.
Sertindole	Potential ↑ in plasma concentrations of sertindole.	Contraindicated due to the risk of QT prolongation (see section 4.3).
Reboxetine	Reboxetine: AUC: ↑ 1.5-fold of both enantiomers	Not recommended because of reboxetine narrow's therapeutic margin.
Quetiapine	Quetiapine: AUC: ↑ 6.2-fold Cmax: ↑ 3.4-fold	Contraindicated as it may increase quetiapine-related toxicity (see section 4.3).
Risperidone	Potential ↑ in AUC of risperidone:	Careful monitoring. Dose adjustment of risperidone may be required.
<i>HIV products</i>		
Maraviroc	Maraviroc: AUC: ↑ 5-fold Cmax: ↑ 3.4-fold	Careful monitoring. Maraviroc dose should be decreased to 150 mg twice daily.
Saquinavir (saquinavir/ritonavir 1000/100 mg bid)	Saquinavir: AUC: ↔ Cmax: ↔ Ketoconazole AUC: ↑ 2.7-fold Cmax: ↑ 1.5-fold (CYP3A4 enzyme inhibition by ritonavir)	Contraindicated due to the risk of QT prolongation (see section 4.3).
Indinavir	Indinavir (600mg TID): AUC: ↓ 1.2-fold Cmin: ↑ 0.7-fold (Relative to Indinavir 800 mg TID alone)	Careful monitoring. Dose reduction of Indinavir to 600 mg every 8 hours should be considered.
Nevirapine	Ketoconazole:	Not recommended

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
	AUC: ↓0.28-fold Cmax: ↓0.56-fold Nevirapine: plasma levels: ↑1.15-1.28-fold compared to historical controls (CYP3A enzyme induction)	
Ritonavir	Ketoconazole: AUC: ↑3.4-fold Cmax: ↑1.6-fold (CYP3A enzyme inhibition)	A dose reduction of ketoconazole should be considered when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. (See also “Effects of other medicinal products on the metabolism of Ketoconazole HRA”).
<i>Beta Blockers</i>		
Nadolol	↑in plasma concentrations of nadolol have been observed	Careful monitoring. Dose adjustment of nadolol may be required.
<i>Calcium Channel Blockers</i>		
Felodipine Nisoldipine	AUC: ↑ has been observed Cmax: ↑ has been observed	Contraindicated due to an increase risk of edema and congestive heart failure (see section 4.3).
Other dihydropyridines Verapamil	Potential ↑in plasma concentrations of these drugs	Careful monitoring. Dose adjustment of dihydropyridines and verapamil may be required.
<i>Cardiovascular Drugs, Miscellaneous</i>		
Ranolazine	Ranolazine: AUC: ↑ 3.0 to 3.9-fold	Contraindicated due to the potential for serious cardiovascular events including QT prolongation (see section 4.3).
Aliskiren	Aliskiren: AUC: ↑ 1.8-fold	Careful monitoring. Dose adjustment of aliskiren may be required.
Bosentan	Bosentan: AUC: ↑ 2-fold Cmax: ↑ 2-fold	Not recommended due to the potential for hepatic toxicity (see section 4.3).
<i>Diuretics</i>		
Eplerenone	Eplerenone: AUC: ↑ 5.5-fold	Contraindicated due to the increased risk of hyperkalaemia and hypotension (see section 4.3).
<i>Gastrointestinal Drugs</i>		
Aprepitant	Aprepitant: AUC: ↑ 5-fold	Careful monitoring. Dose adjustment of aprepitant may be required
Domperidone	Domperidone: AUC: ↑ 3.0 fold Cmax: ↑ 3.0 fold	Not recommended due to an increased risk in QT prolongation.
<i>Immunosuppressants</i>		
Everolimus Sirolimus (rapamycin)	Everolimus: AUC: ↑ 15.3-fold Cmax: ↑ 4.1-fold Sirolimus (rapamycin): AUC: ↑ 10.9-fold	Contraindicated due to the large increase in these drugs concentrations (see section 4.3).

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
	Cmax: ↑ 4.4-fold	
Temsirolimus Tacrolimus Ciclosporine Budesonide Ciclesonide	Temsirolimus: AUC: ↔ Cmax: ↔ Ciclesonide active metabolite: AUC: ↑ 3.5-fold Rest of drugs ↑in plasma concentrations of these drugs have been observed	Not recommended unless necessary. Careful monitoring and dose adjustment of these drugs may be required.
Dexamethasone, fluticasone, methylprednisolone	Potential ↑in plasma concentrations of these drugs	Careful monitoring. Dose adjustment of these drugs may be required.
<i>Lipid Lowering Drugs</i>		
Lovastatin, simvastatin, atorvastatin*	Potential ↑in plasma concentrations of these drugs	Contraindicated due to an increased risk of skeletal muscle toxicity, including rhabdomyolysis (see section 4.3).
<i>Respiratory Drugs</i>		
Salmeterol	Salmeterol AUC: ↑ 15-fold Cmax: ↑ 1.4-fold	Not recommended due to an increased risk in QT prolongation.
<i>Urological Drugs</i>		
Fesoterodine Tolterodine Solifenacin	Fesoterodine active metabolite: AUC: ↑ 2.3-fold Cmax: ↑ 2.0-fold Solifenacin: AUC: ↑ 3.0-fold ↑in plasma concentrations of tolterodine have been observed	Not recommended due to an increased risk of QT prolongation. Fesoterodine and solifenacin are contraindicated in patients with renal impairment (see section 4.3).
<i>Phosphodiesterase(PD E5) inhibitors</i>		
Sildenafil Tadalafil Vardenafil	Tadalafil: AUC: ↑ 4-fold Cmax: ↑ 1.2-fold Vardenafil: AUC: ↑ 10-fold Cmax: ↑ 4-fold Potential ↑in plasma concentrations of sildenafil	Not recommended due to the increased risk of adverse events. Vardenafil is contraindicated in men older than 75 years old (see section 4.3).
<i>Other</i>		
Colchicine	↑in plasma concentrations of colchicine have been observed	Not recommended due to a potential increase in colchicine-related toxicity. Contraindicated in patients with renal impairment (see section 4.3).
Tolvaptan	↑in plasma concentrations of tolvaptan have been observed	Contraindicated due to an increase in the plasma concentrations (see section 4.3).
Cinacalcet	Cinacalcet	Careful monitoring.

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
	AUC: ↑ 2 fold Cmax: ↑ 2 fold	Dose adjustment of cinacalcet may be required.
Ebastine	↑in plasma concentrations of ebastine have been observed	Not recommended due to an increased risk in QT prolongation.
Mizolastine Halofantrine	Potential ↑in plasma concentrations of these drugs	Contraindicated due to the potential for serious cardiovascular events including QT prolongation (see section 4.3).

* Rosuvastatin is not a CYP 3A4 substrate. Ketoconazole HRA did not produce any change in rosuvastatin pharmacokinetics, therefore, co-administration of Ketoconazole HRA and rosuvastatin is unlikely to increase the risk of toxicity of rosuvastatin. Other statins that are not CYP3A4 substrates (pravastatin and fluvastatin) can be co-administered with Ketoconazole HRA.

Other interactions

Exceptional cases of a disulfiram-like reaction have been reported when ketoconazole was co-administered with alcohol, characterised by flushing, rash, peripheral oedema, nausea and headache, have been reported. All symptoms resolved completely within a few hours.

Co-administration of ketoconazole and pasireotide is not recommended since the combination can lead to a QT prolongation in patients with known cardiac rhythm disorders.

There is no evidence to suggest that there is an interaction between Ketoconazole HRA and other steroidogenesis inhibitors (ie metyrapone).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are insufficient clinical data regarding the use of Ketoconazole HRA in pregnant women. Preclinical data show that Ketoconazole HRA crosses the placenta and is teratogenic. Ketoconazole HRA is contraindicated during pregnancy and it should not be used in women of childbearing potential not using an effective method of contraception (see section 4.3).

Breast-feeding

Since ketoconazole is excreted in the milk, mothers who are under treatment must not breast-feed whilst being treated with Ketoconazole HRA (see section 4.3).

Fertility

Studies in animals have shown effects on male and female reproductive parameters (see section 5.3).

4.7 Effects on ability to drive and use machines

No specific studies have been conducted to assess the effect of ketoconazole on the ability to drive or use machines. Patients should be warned about the potential for dizziness and somnolence (see section 4.8) and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions are adrenal insufficiency, nausea, vomiting, abdominal pain, diarrhoea, pruritus, rash and the hepatic enzymes increased.

The most serious adverse reaction is hepatotoxicity, primarily as acute hepatocellular toxicity but may also result in cholestatic injury or a mixed pattern of toxicity. ASAT, ALAT, gammaGT, bilirubin and alkaline phosphatase should be monitored at frequent intervals during treatment (see sections 4.2 and 4.4).

Tabulated list of adverse reactions

The safety of Ketoconazole HRA has been evaluated based on published literature and use of ketoconazole as an antifungal treatment.

The adverse reactions listed below in table 2 are classified according to System Organ Class. Frequency groupings are defined according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon: ($\geq 1/1,000$ to $< 1/100$), rare: ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known: cannot be estimated from the available data.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: Incidence of adverse reactions and marked laboratory abnormalities reported in the literature in adults and adolescents patients

System organ class	Frequency	Adverse reaction
<i>Blood and lymphatic system disorders</i>	Uncommon	Thrombocytopenia
<i>Immune system disorders</i>	Uncommon	Allergic conditions including anaphylactic shock, anaphylactoid reaction and anaphylactic reaction and angioedema
<i>Endocrine disorders</i>	Common	Adrenal insufficiency
<i>Psychiatric disorders</i>	Not Known	Insomnia, nervousness
<i>Metabolism and nutrition disorders</i>	Not known	Alcohol intolerance, anorexia, increased appetite
<i>Nervous system disorders</i>	Uncommon	Headache, dizziness, somnolence
	Not known	Intracranial pressure increased (papilloedema, fontanelle bulging), paraesthesia
<i>Eye disorders</i>	Not known	Photophobia
<i>Respiratory, thoracic and mediastinal disorders</i>	Not known	Epistaxis
<i>Gastrointestinal disorders</i>	Common	Nausea, abdominal pain, vomiting, diarrhoea
	Not known	Dyspepsia, flatulence, tongue discoloration, dry mouth, dysgeusia
<i>Hepatobiliary disorders</i>	Very common	Liver function tests abnormal
	Rare	Serious hepatotoxicity, including jaundice, hepatitis, hepatic necrosis, hepatic cirrhosis, hepatic failure including cases necessitating transplantation or resulting in death. (see 4.4 Special warnings and special precautions for use)
<i>Skin and subcutaneous tissue disorders</i>	Common	Pruritus, rash
	Uncommon	Urticaria, alopecia
	Not known	Photosensitivity, erythema multiforme,

		dermatitis, erythema, , xeroderma
<i>Musculoskeletal and connective tissue disorder</i>	Not known	Myalgia, arthralgia
<i>Reproductive system and breast disorders</i>	Not known	Menstrual disorder, azoospermia, erectile dysfunction, gynaecomastia
<i>General disorders and administration site conditions</i>	Uncommon	Asthenia
	Very rare Not known	Pyrexia Oedema peripheral, malaise, hot flush
<i>Investigations</i>	Very common	Hepatic enzyme increased
	Uncommon	Platelet count decreased
	Not known	Transient decrease of testosterone concentrations

Description of selected adverse reactions

Hepatotoxicity

Serious hepatic toxicity caused by ketoconazole treatment is rare (1/15000). Acute hepatocellular injury has been primarily observed as has cholestatic injury or a mixed pattern of toxicity. Fatal cases have been reported particularly when treatment is continued despite liver enzyme elevation. Increases in liver enzymes ($\leq 5N$ and $> 5N$) were observed in ~13.5 % and ~2.5% of patients respectively occurring mostly within the first 6 months of treatment. Liver enzyme levels returned to normal within 2-12 weeks after a dose decrease or withdrawal of ketoconazole. Hepatotoxicity does not appear to be dose dependent. All potential associated factors of hepatotoxicity, and abnormal liver enzyme levels detected before Ketoconazole HRA initiation, should be taken into account before considering Ketoconazole HRA treatment. Ketoconazole HRA should not be administered when liver enzymes are greater than 2 times the upper limit of normal or in association with other hepatotoxic drugs. Liver enzyme monitoring should be performed once weekly during the first month of treatment and then monthly for 6 months. In the case an increase of liver enzymes is detected which is less than 3 times the upper limit of normal, closer monitoring of liver function should be performed and the daily dose should be decreased by at least 200 mg. In the case of increase of liver enzymes levels above 3 times the upper limit of normal, Ketoconazole HRA should be stopped immediately and should not be reintroduced because of the risk of serious hepatic toxicity.

Adrenal Insufficiency

Adrenal insufficiency may occur in patients on ketoconazole without corticosteroid substitution (block-only regimen) or if there is an insufficient glucocorticoid replacement therapy (for the patients treated with a block-and-replace regimen). Monitor and instruct patients on the signs and symptoms associated with hypocortisolism (e.g. weakness, fatigue, anorexia, nausea, vomiting, hypotension, hyperkalemia, hyponatraemia, hyperkalaemia or hypoglycaemia). Adrenal insufficiency may be detected by periodic clinical assessment and monitoring of plasma/serum or salivary cortisol levels. In case of adrenal insufficiency, Ketoconazole HRA treatment should be temporarily discontinued or the dose reduced and, if needed, a corticosteroid substitution therapy added.

Paediatric population

Frequency of hepatotoxicity could be higher in adolescents than in adults. In the literature, among 24 paediatric patients treated with ketoconazole, two developed severe hepatotoxicity. A 14 year-old girl who was treated for Cushing's disease with ketoconazole 200 mg twice daily presented one month later with jaundice, fever anorexia, nausea and vomiting. Ketoconazole was stopped but she deteriorated rapidly and died. A 17 years old girl was treated on ketoconazole 1200 mg/day for an adrenal carcinoma with liver metastasis and had altered liver function tests at 22 days. After ketoconazole withdrawal, liver enzymes returned to normal levels within 3 weeks (section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

There is no known antidote to Ketoconazole HRA. The maximal dose that was used for treatment of Cushing's syndrome is 1600 mg/day.

In the event of accidental overdose, treatment consists of supportive measures. Within the first hour after ingestion gastric lavage may be performed. Activated charcoal may be given if considered appropriate.

In the case of signs suggestive of an adrenal insufficiency, in addition to the general measures to eliminate the drug and reduce its absorption, a 100 mg dose of hydrocortisone should be administered at once, together with saline and glucose infusions. Close surveillance will be necessary: blood pressure and fluid and electrolyte balance should be monitored for a few days.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not yet assigned, ATC code: Not yet assigned

Mechanism of action

Ketoconazole is a steroidogenesis inhibitor. Ketoconazole is an imidazole derivative that is a potent inhibitor of cortisol synthesis resulting from its ability to inhibit several cytochrome P450 enzymes in the adrenal glands. Ketoconazole inhibits primarily the activity of 17 α -hydroxylase, but it also inhibits 11-hydroxylation steps, and at higher doses the cholesterol side-chain cleavage enzyme. Therefore, ketoconazole is an inhibitor of cortisol and aldosterone synthesis. Ketoconazole is also a potent inhibitor of androgens synthesis, inhibiting the activity of C17-20 lyase in the adrenals and also in Leydig cells.

Apart from adrenal blocking effect, ketoconazole may also have direct effects on corticotropic tumour cells in patients with Cushing's disease.

Clinical efficacy

The efficacy and safety of ketoconazole in the treatment of Cushing's syndrome from all causes have been described through several published retrospective studies, chart reviews and case reports. Control of cortisol levels, either in serum/plasma or urine, was used to assess the efficacy of the treatment, along with the evaluation of clinical symptoms of Cushing's syndrome. More than 800 patients have been treated with ketoconazole with variable treatment duration and modalities. About 200 patients were treated for more than 6 months and some of them were treated for several years.

Urinary free cortisol (UFC) levels were normalised in about 50% of patients on ketoconazole. Response rates varied between 43 and 80% depending on the studies and the criteria to define a response. About 75% of patients achieved a decrease of more than 50% of UFC levels on ketoconazole, compared to pre-treatment levels

Combination therapy

Ketoconazole has been used both as sole medical therapy and in combination with other drugs, mainly with metyrapone, in patients with more severe disease or in those not completely responding to a single agent or in those requiring a dose reduction of at least one of the drugs to improve tolerance. Ketoconazole has also been used with other therapies including surgery and pituitary radiation. Overall, ketoconazole was shown to be an effective drug for normalising cortisol levels in all causes of Cushing's syndrome and, if tolerated, ketoconazole treatment can be maintained for a long period.

Escape phenomenon

In approximately 10 to 15 % of ketoconazole treated patients, an "escape phenomenon" is observed and reinforces the need for a long-term clinical and biochemical follow-up of these patients. If such a

phenomenon occurs, a further dose increase may be required to maintain cortisol levels within the normal range.

Use in Cushing's disease

Data from 535 patients with Cushing's disease treated with ketoconazole, along with 13 individual case reports are available in the literature. In a retrospective study conducted in several French centres, 200 patients with Cushing's disease were followed between 1995 and 2012. At the last visit, 78 patients (49.3%) were controlled, 37 patients (23.4%) had partial control with at least 50% decrease of UFC (without normalisation), and 43 patients (27.2%) had unchanged UFC levels. At the last follow-up, clinical signs were improved in 74/134 patients (55.2%), hypertension in 36/90 patients (40%), hypokalaemia in 10/26 patients (38.4%), and diabetes mellitus in 23/39 patients (59%).

Use in ectopic ACTH syndrome

Data from 91 patients with the ectopic ACTH syndrome treated with ketoconazole were reviewed, along with 18 individual case reports. In a Canadian study, of the 12 assessable patients (out of 15), 10 showed a reduction in urinary free cortisol levels, but only five had complete resolution on ketoconazole doses 400 to 1200 mg/day. Clinical improvement in hypokalaemia, metabolic alkalosis, diabetes mellitus, and hypertension occurred even in the absence of complete hormonal response.

Use in ACTH-independent Cushing's syndrome

Data from 17 patients with adrenal tumours and from 2 patients with primary nodular adrenocortical hyperplasia (NAH) treated with ketoconazole are available in the literature along with 17 individual case reports of patients with benign or malignant tumours or NAH and 2 paediatric cases of McCune Albright syndrome. Improvement of clinical symptoms was noted in most patients after initiation of treatment. However in patients with adrenal cortical carcinoma, improvement of hypercortisolism on ketoconazole was limited in some cases.

Paediatric population

Data on 24 paediatric patients with endogenous Cushing's syndrome treated with ketoconazole are available in the literature, among which 16 were aged over 12 years old and 8 were aged less than 12 years old. Treatment with ketoconazole in paediatric patients allowed normalisation of urinary free cortisol levels and clinical improvement, including recovering of growth rate and gonadal function, normalisation of blood pressure, Cushing's syndrome features and weight loss in most of the cases. The doses used in adolescents above 12 years old were similar to the doses used in adults' patients with endogenous Cushing's syndrome.

5.2 Pharmacokinetic properties

Absorption

Ketoconazole is a weak dibasic agent and thus requires acidity for dissolution and absorption. Mean peak plasma concentrations of approximately 3.5 µg/ml are reached within 1 to 2 hours, following oral administration of a single 200 mg dose taken with a meal.

C_{max} and AUC increase more than proportionally with dose. At steady state, mean peak concentrations of 1.7µg/mL to 15.6µg/mL were reported for total daily doses of 200mg to 1200mg.

Distribution

In vitro, the plasma protein binding is about 99% mainly to the albumin fraction. Ketoconazole is widely distributed into tissues; however, only a negligible proportion of ketoconazole reaches the cerebral-spinal fluid.

Biotransformation

Ketoconazole is extensively metabolised to a large number of inactive metabolites. In vitro studies have shown that CYP3A4 is the major enzyme involved in the metabolism of ketoconazole.

The major identified metabolic pathways are oxidation and degradation of the imidazole and piperazine rings, oxidative O-dealkylation and aromatic hydroxylation.

Ketoconazole is a potent inhibitor of CYP3A4 and P-gp. Ketoconazole has not been demonstrated to induce its own metabolism.

Elimination

Plasma elimination is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. The half-life of ketoconazole increases with dose and duration of treatment. At doses > 400 mg/day, half-lives of 3 to 10 hours have been reported. About 13% of the dose is excreted in the urine, of which 2 to 4% is unchanged drug. The major route of excretion is through the bile into the intestinal tract.

Special population

Paediatrics

Based on limited data, pharmacokinetics parameters (AUC, C_{max} and half-life) of ketoconazole for doses of 5 to 10 mg/kg/days, corresponding approximately to daily doses of 200-800 mg, are similar in paediatric and adult population.

Renal impairment

The pharmacokinetics of ketoconazole were not significantly different in patients with renal failure compared to healthy subjects.

Elderly patients

No formal evaluation of the effect of age on the pharmacokinetics of Ketoconazole HRA has been performed. There are no data suggesting a need for a specific dose adjustment in this population.

5.3 Preclinical safety data

The toxicological profile of ketoconazole has been established from long term studies in rats and dogs.

Bone fragility and broken legs were reported in rats but were not observed in other species.

Consistent with the pharmacological action of ketoconazole, effects were observed on adrenal and gonads in rats and dogs.

Elevated liver enzymes and histological changes in the liver consisting in dose-related lipofuscin accumulation in hepatocytes were reported in rats and dogs after repeated administration of ketoconazole.

Electrophysiological studies have shown that ketoconazole inhibits the rapidly activating component of the cardiac delayed rectifier potassium current, prolongs the action potential duration, and may prolong the QT interval. However no modifications of ECG were recorded in dogs at daily doses up to 40 mg/kg administered for 12 months.

Ketoconazole was not genotoxic in vitro and in vivo. However, the genotoxic potential was not properly determined for the proposed dosing regimen in the treatment of endogenous Cushing's syndrome. Ketoconazole is not carcinogenic.

In reproduction studies, ketoconazole impaired fertility in males and females. Doses of 25 mg/kg and higher in male rats and dogs produced sperm abnormalities and decreased fertility in rats. Ketoconazole at doses up to 40 mg/kg had no effects on female fertility in the rat, whilst doses of 75 mg/kg and higher decreased the pregnancy rate and the number of implantation sites. Doses of 80 and 160 mg/kg inhibited ovulation in immature rats. Ketoconazole at doses of 40 mg/kg/day and higher produces evidence of embryotoxicity and teratogenicity in rats and rabbits. Observed teratogenic effects were mainly skeletal anomalies, including cleft palate, brachydactylia, ectrodactylia and syndactylia. Treatment of juvenile rats for 30 day beginning at 21 days of age delayed the puberty onset. Effects on human reproduction cannot be excluded.

Studies in pregnant rats and in guinea pigs with ³H-ketoconazole indicate that ketoconazole crosses the placenta.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Povidone
Microcrystalline cellulose
Silica colloidal
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Alu blister of 10 tablets
Pack sizes containing 6 blisters of 10 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Laboratoire HRA Pharma
15 rue Béranger
75003 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/965

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Polfarmex S.A.
ul. Jozefow 9
99-300 Kutno
Poland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription

(see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
A Post Authorisation safety study : Multi-country, observational registry to collect clinical information on patients with Cushing Syndrome patients exposed with Ketoconazole (preferably using the existing European Registry on Cushing’s syndrome (ERCUSYN) registry where feasible), to assess drug utilization patterns and to document the safety (eg hepatotoxicity, QT prolongation) and effectiveness of	Yearly submission

ketoconazole	
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ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ketoconazole HRA 200 mg tablets
ketoconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg of ketoconazole.

3. LIST OF EXCIPIENTS

Contains lactose.
See the package leaflet or further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Laboratoire HRA Pharma
15 rue béranger
75003 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/965

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ketoconazole HRA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ketoconazole HRA 200 mg tablets
ketoconazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

HRA Pharma

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ketoconazole HRA 200 mg tablets

Ketoconazole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ketoconazole HRA is and what it is used for
2. What you need to know before you take Ketoconazole HRA
3. How to take Ketoconazole HRA
4. Possible side effects
5. How to store Ketoconazole HRA
6. Contents of the pack and other information

1. What Ketoconazole HRA is and what it is used for

Ketoconazole HRA is a medicine that contains the active substance ketoconazole. It is used to treat endogenous Cushing's syndrome (when the body produces an excess of cortisol) in adults and adolescents above the age of 12 years.

Cushing's syndrome is caused by overproduction of a hormone called cortisol which is produced by the adrenal glands. Ketoconazole HRA is able to inhibit the activity of the enzymes responsible for the synthesis of cortisol and consequently is able to decrease the over-production of cortisol by your body and to improve the symptoms of Cushing's syndrome.

2. What you need to know before you take Ketoconazole HRA

Do not take Ketoconazole HRA

- if you are allergic to ketoconazole and/or to any imidazole antifungal, or to any of the other ingredients (listed in section 6)
- if you have liver problems
- if you are pregnant
- if you are breastfeeding
- if you have a history of an irregular heart beat
- if you are taking any of the following medicines:
 - certain medicines for lowering blood cholesterol: simvastatin, atorvastatin, lovastatin
 - certain heart medicines: epleronone, dronedarone, disopyramide, felodipine, nisoldipine, ranolazine
 - certain medicines used for the treatment of the paludism: quinidine, halofantrine
 - certain medicines used for severe mental health disorders and severe depression: pimozide, sertindole, lurasidone, quetiapine
 - certain medicines used for the allergies: mizolastine

- dabigatran – medicine used to prevent the formation of blood clots
- certain medicines to help to sleep and for anxiety: triazolam, alprazolam, midazolam (taken by mouth)
- certain medicines used for migraine attacks: dihydroergotamine, ergometrine (ergonovine) ergotamine and methylergometrine (methylergonovine)
- certain medicines used in cancers: irinotecan, everolimus
- sirolimus: used to prevent your body from rejecting a kidney transplant
- tolvaptan used for a specific disease called “syndrome of inappropriate antidiuretic hormone secretion”
- vardenafil in men older than 75 years – medicine to treat erectile dysfunction in adults men
- certain medicines for HIV: saquinavir/ritonavir, saquinavir
- methadone: medicine to treat dependence to drugs
- In patients with renal disorders:
 - colchicine: medicine to treat gout
 - fesoterodine and solifenacin: medicines to treat the symptoms of an overactive bladder
 - telithromycin and clarithromycin: medicine used to treat infections

Do not take Ketoconazole HRA if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Ketoconazole HRA.

Warnings and precautions

Talk to your doctor or pharmacist before taking Ketoconazole HRA.

Liver disease

Speak with your doctor if you have a history of liver disease. You should know that your liver enzyme tests will be regularly monitored before starting the treatment, once weekly during the first month after Ketoconazole HRA initiation and then monthly for 6 months due to the risk of serious hepatic toxicity. They will be checked again after that in case your doctor increases your daily ketoconazole dose. **You should stop your treatment and contact your doctor immediately if you feel unwell or experience symptoms such as lack of appetite, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine.**

Specific dosing regimen

If you take concomitant glucocorticoid replacement therapy with your Ketoconazole HRA treatment, your doctor should inform you how to adapt your glucocorticoid replacement therapy dose if you are under stress or have surgery or an infection. In addition, you should receive an emergency card and should be equipped with an emergency glucocorticoid set.

Adrenal function

Your adrenal function will be monitored at regular intervals as this is the standard care in the follow-up of Cushing’s syndrome therapy and since adrenal insufficiency can occur during the treatment. You should contact your doctor immediately if you have symptoms such as weakness, fatigue, lack of appetite, nausea, vomiting or low blood pressure.

Heart disease

Ketoconazole HRA can change how your heart beats – this can be serious. **Contact your doctor immediately, if you get palpitations or an irregular heartbeat during treatment.**

Gastric acidity

You should not take antacids (eg aluminium hydroxide) or other medicines for acid indigestion for at least 2 hours after the intake of Ketoconazole HRA.

Use with pasireotide

Tell your doctor if you are taking pasireotide, another drug used to treat a subset of the Cushing’s syndrome because it can lead to severe side effects in patients suffering from cardiac disorders.

Coexisting inflammatory/autoimmune disorders

Tell your doctor if you suffer from an autoimmune disorder, you will be closely supervised.

Ketoconazole HRA with alcohol

Do not drink alcohol while taking Ketoconazole HRA since it could lead to a disulfiram-like reaction (a very uncomfortable reaction characterized especially by severe flushing).

Children and adolescents

This medicine is not recommended for children under 12 years due to the lack of data in these patients.

Other medicinal products and Ketoconazole HRA

Tell your doctor or pharmacist if you are taking, or have recently taken or might take any other medicines. **There are some medications that must not be taken with Ketoconazole HRA (see section 2).** Ask your doctor or pharmacist for more information if you are taking Ketoconazole HRA with other medicines.

Medicines that can interact with Ketoconazole HRA include:

- oral medicines for anticoagulation (taken by mouth): rivaroxaban, cilostazol, warfarin and others coumarin like
- HIV medicines such as maraviroc, indinavir, nevirapine, ritonavir
- certain medicines used for cancer such as vinca alkaloids, busulfan, docetaxel, erlotinib, imatinib, dasatinib, sunitinib, lapatinib, nilotinib, bortezomib, paclitaxel, vincristine, vinblastine
- certain medicines used to treat infections: rifabutin, telithromycin, rifampicin, isoniazide, clarithromycin
- certain antidiabetics: repaglinide, saxagliptin
- certain medicines used for mental disorders: buspirone, aripipazole, haloperidol, reboxetine, risperidone
- certain heart medicines – verapamil, digoxin, nadolol, aliskiren
- certain anticonvulsivants: carbamazepine, phenitoïn
- certain glucocorticoids – such as budesonide, fluticasone, dexamethasone, methylprednisolone, ciclesonide
- certain strong painkillers (narcotics) – such as alfentanyl, fentanyl, buprenorphine (injection and sublingual), oxycodone
- certain medicines used for nausea and vomiting: domperidone, aprepitant
- others: sildenafil, solifenacin, tolterodine, mitotane, praziquantel, eletriptan, fesoterodine, salmeterol, bosentan, midazolam (by injection), tadalafil, vardenafil, temsirolimus, cinalcacet, tacrolimus, ebastine, ciclosporine, colchicine

You should not take antacids (eg aluminium hydroxide) or other medicines for acid indigestion for at least 2 hours after the intake of Ketoconazole HRA (see section Warning and Precautions).

Pregnancy, breast-feeding and fertility

Do not take this medicinal product during pregnancy. If you think you are pregnant or are planning to become pregnant, ask your doctor for advice.

Do not breastfeed your baby if you are taking Ketoconazole HRA.

Driving and using machines

Dizziness or somnolence have been reported during treatment with Ketoconazole HRA. Do not drive or operate machines if you experience these symptoms.

Ketoconazole HRA contains lactose

If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Ketoconazole HRA

Initiation and follow up of the treatment must be supervised by specialists in endocrinology.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will test your blood before you start the treatment and regularly during the treatment to detect any possible abnormalities and also to measure the levels of cortisol. The dose will be adapted to your condition with the aim to restore normal cortisol levels.

The recommended initial dose is usually 600 mg per day taken orally (3 tablets per day in 3 divided times). A daily dose from 400 mg per day (2 tablets) to 1200 mg per day (6 tablets) taken orally in 2 to 3 divided doses may be required to restore your normal cortisol levels.

If you take more Ketoconazole HRA than you should

If you have taken more than the prescribed dose of Ketoconazole HRA, you must contact your doctor immediately.

If you forget to take Ketoconazole HRA

Do not take a double dose to make up for a forgotten dose. If you forget to take one dose, take this dose as soon as you remember. Then go on with regular schedule as prescribed. Do not change the prescribed dose yourself.

If you stop taking Ketoconazole HRA

If you interrupt your treatment with Ketoconazole HRA your cortisol level may increase again and your symptoms may come back. Therefore, do not stop taking Ketoconazole HRA unless your doctor tells you.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects may be serious. Liver problems can rarely happen (may affect up to 1 in 1,000 people). Stop taking Ketoconazole HRA and tell your doctor straight away if you experience any of the following:

- long-lasting severe headache or blurred vision
- severe lack of appetite (anorexia)
- weight loss
- nausea or vomiting
- unusual tiredness or fever
- stomach pain
- muscle weakness
- yellowing of the skin or whites of the eyes
- unusually dark urine or pale stools

Adrenal insufficiency may occur and can be a serious side effect. Ketoconazole HRA may temporarily lower the amount of hormones produced by your adrenal gland (cortisol) to below the normal range but your doctor will correct this using appropriate hormone medication or by adjusting the dose of Ketoconazole HRA. You should contact your doctor immediately if you have symptoms such as weakness, fatigue, loss of appetite, nausea, vomiting, low blood pressure.

Very common side effects (may affect more than 1 in 10 people):

- An elevated levels of liver enzymes in your blood

Common side effects (may affect up to 1 in 10 people):

- Adrenal insufficiency (diminution of the amount of hormones (cortisol))
- Nausea
- Abdominal pain
- Vomiting
- Diarrhoea
- Skin reactions (pruritus, rash)

Uncommon side effects (may affect up to 1 in 100 people):

- Allergic reactions which can, rarely, be serious
- Change in laboratory markers
- Platelet count decreased
- Headache
- Dizziness
- Sleepiness
- Skin reactions (urticarial)
- Hair loss
- Fatigue

Rare side effects (may affect up to 1 in 1,000 people):

- Serious liver problems

Very rare side effects (may affect up to 1 in 10,000 people):

- Pyrexia (fever)

Side effects with frequency not known (frequency cannot be estimated from the available data):

- Insomnia
- Nervousness
- Intolerance to alcohol
- Loss of appetite or increased appetite
- Intracranial pressure increased
- Sensation of tingling or pricking
- Aversion to light
- Bleeding from the nose
- Dyspepsia (impaired digestion)
- Flatulence
- Tongue discoloration
- Dry mouth
- Distortion of the sense of taste
- Redness of the skin
- Myalgia (muscle pain)
- Arthralgia (joint pain)
- Menstrual disorders
- Azoospermia (no sperm count)
- Erectile dysfunction
- Gynaecomastia (enlargement in breast tissues in male)
- Oedema peripheral (dropsy in extremities)
- Malaise
- Hot flush
- Transient decrease of testosterone, a male hormone (androgen) made by the body, mostly produced in the testes

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ketoconazole HRA

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and on the blister after EXP. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ketoconazole HRA 200 mg tablets contains

- The active substance is ketoconazole.
- The other ingredients are maize starch, lactose monohydrate, povidone, microcrystalline cellulose, silica colloidal, magnesium stearate

What Ketoconazole HRA 200 mg tablets looks like and contents of the pack

Ketoconazole HRA is available in pack containing 60 tablets.

Marketing Authorisation Holder

Laboratoire HRA Pharma
15 rue béranger
75003 Paris
France

Manufacturer

Polfarmex S.A.
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99-300 Kutno
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.