SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 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 800-1,200 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 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 1,200 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 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 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 can be reintroduced thereafter at a lower dose (see section 4.4);
- Treatment with ketoconazole can be stopped abruptly without a need for progressive dose decrease where a change in the therapeutic strategy (e.g. 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:

    - weekly for one month after initiation of the treatment
    - then monthly for 6 months
    - 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 should be stopped immediately and should not be reintroduced due to the risk of serious hepatic toxicity. Ketoconazole 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 may be continued as described above;
- Block-and-replace regimen: the maintenance dose of ketoconazole should be further increased by 200 mg and concomitant corticosteroid replacement therapy should be added (see section 4.4).

Special populations

Elderly patients
Data on the use of ketoconazole 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).

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

Hepatic impairment
Ketoconazole is contraindicated in patients with acute or chronic hepatic impairment (see sections 4.3, 4.4 and 5.3). The treatment must not be initiated in patients with liver enzymes levels above 2 times the upper limit of normal

Paediatric population
The safety and efficacy of Ketoconazole HRA in children aged less than 12 years have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- Hypersensitivity to any imidazole antifungal medicinal product;
- 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):
- Pregnancy (see section 4.6);
- Breastfeeding (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 (see section 4.5):
    - CYP3A4 metabolised HMG-CoA reductase inhibitors (e.g. simvastatin, atorvastatin and lovastatin) due to an increased risk of skeletal muscle toxicity including rhabdomyolysis;
    - eplerenone due to an increased risk of hyperkalemia and hypotension;
    - 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;
    - dabigatran due to an increased bleeding risk;
    - 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 reactions;
    - 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 reactions;
- paritaprevir/ombitasvir (ritonavir) due to increased risk of adverse reactions;
- fesoterodine and solifenacin in patients with renal impairment;
- tolvaptan used for a specific disease called "syndrome of inappropriate antidiuretic hormone secretion".

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. 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 insuficiency 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 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 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 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 should be temporarily discontinued or the dose reduced and if necessary corticosteroid substitution should be initiated. Ketoconazole 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
- Within one week after the beginning of the treatment
- As clinically indicated thereafter.

In case of co-administration of an medicinal product 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. 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 with an acidic beverage e.g. cola beverage, orange juice.
If acid secretion suppressors are added to or removed from the concomitant medicinal products then ketoconazole dose should be adjusted according to cortisol levels.

Potential interaction with medicinal products

Ketoconazole has a high potential for clinically important medicinal products interactions.
Ketoconazole is mainly metabolised through CYP3A4. Coadministration of potent enzyme inducers of CYP3A4 may decrease the bioavailibity of ketoconazole. 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 is a potent inhibitor of CYP3A4: inhibition of CYP3A4 by ketoconazole can increase patients' exposure to a number of medicinal products which are metabolised through this enzymatic system (see section 4.5).

Ketoconazole is also a potent inhibitor of P-gp: inhibition of P-gp by ketoconazole 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 or not recommended depending on the observed or expected effect with ketoconazole (i.e. resulting in augmentation of the plasma concentration, AUC, C_{max} of the drugs) and the known therapeutic margins of the drugs. Some combinations may lead to an increased risk of ventricular tachyarrhythmias, including occurrences of torsade de pointes, a potentially fatal arrhythmia (see Table 1 Interactions and recommendations for co-administration, section 4.5).

Use with hepatotoxic medicinal products
Co-administration of ketoconazole and other medicinal products 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 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 galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant therapy with medicinal products that are contraindicated during treatment with ketoconazole and resulting in potentially life-threatening adverse reactions :

- CYP3A4 metabolised HMG-CoA reductase inhibitors (e.g. simvastatin, atorvastatin and lovastatin) due to an increased risk of skeletal muscle toxicity including rhabdomyolysis;
- eplerenone due to an increased risk of hyperkalemia and hypotension;
- 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;
- dabigatran due to an increased bleeding risk;
- 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 reactionsevents
- 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 reactions
- paritaprevir/ombitasvir (ritonavir) due to increased risk of adverse reactions;
- fesoterodine and solifenacin in patients with renal impairment;
- tolvaptan used for a specific disease called "syndrome of inappropriate antidiuretic hormone secretion".

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

Medicinal products affecting the absorption of ketoconazole

Medicinal products affecting gastric acidity impair the absorption of ketoconazole (see section 4.4).

Effects of other medicinal products on the metabolism of ketoconazole

Ketoconazole is mainly metabolised by cytochrome CYP3A4.
Enzyme-inducing medicinal products such as rifampicin, rifabutin, carbamazepine, isoniazid, nevirapine, mitotane and phenytoin may significantly reduce the bioavailability of ketoconazole. Use of ketoconazole 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, these medicinal products should be used with caution when co-administered with ketoconazole and patients should be monitored closely for signs and symptoms of adrenal insuficiency. Ketoconazole dose should be adjusted accordingly.

Effects of ketoconazole on the metabolism of the other medicinal products

- Ketoconazole is a potent inhibitor of CYP3A4 and can inhibit the metabolism of medicinal products metabolised by this enzyme. This can result in an increase and/or prolongation of their effects, including adverse reactions.
- *In vitro* data indicate that ketoconazole is an inhibitor of CYP1A2 and does not significantly inhibit CYP 2A6 and 2E1. At clinically relevant concentrations inhibition of CYP2B6, 2C9/C8, 2C19 and 2D6 by ketoconazole cannot be excluded.
- Ketoconazole can inhibit the transport of medicinal products by P-gp, which may result in an increased plasma concentration of these medicinal products.
- Ketoconazole inhibits BCRP (Breast Cancer Resistance Protein) in *in vitro* studies. Data of inhibition indicate that risk of interaction with BCRP substrates cannot be excluded at the systemic level with very high doses of ketoconazole. 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 medicinal products

Medicinal product by therapeutic area	**Expected effect on drug levels**	**Recommendation for co-administration**
Analgesic opioid		
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 C_{max}: ↑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 reactions (respiratory depression, sedation) is recommended. It may be necessary to lower the dose of alfentanil and fentanyl.
Oxycodone	↑in plasma concentrations of oxycodone have been observed	Careful monitoring. The oxycodone dose may be adjusted.

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
Antiarrhythmics		
Disopyramide Quinidine Dronedarone	Potential ↑in plasma concentrations of disopyramide and quinidine Repeated doses of 200 mg ketoconazole daily resulted in a 17-fold increase in dronedarone exposure	Contraindicated due to the risk of serious cardiovascular events including QT prolongation (see section 4.3).
Digoxin	Potential ↑in plasma concentrations of digoxine	Careful monitoring of digoxin levels is recommended.
Anticoagulants and antiplatelet drugs		
Dabigatran	Dabigatran: AUC: ↑ 2.6-fold C_{max}: ↑2.5-fold	Contraindicated due to an increased bleeding risk (see section 4.3).
Rivaroxaban	Rivaroxaban: AUC: ↑ 2.6-fold C_{max}: ↑1.7-fold	Not recommended due to an increased bleeding risk.
Apixaban	Apixaban AUC: ↑ 2-fold C_{max}: ↑1.6-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 dose of 50 mg twice daily is recommended in combination with ketoconazole.
Warfarin and other coumarin-like drugs	Potential ↑in plasma concentrations of warfarin	Careful monitoring INR (international normalised ratio) monitoring recommended.
Edoxaban	AUC: ↑ 1.8-fold C_{max}: ↑ 1.8-fold	Dose of edoxaban needs to be reduced when used concomitantly, please consult edoxaban SmPC.
Anticonvulsants		
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 ").
Antidiabetics		
Repaglinide	Repaglinide: AUC: ↑ 1.2-fold C_{max}: ↑ 1.2-fold	Careful monitoring. Dose adjustement of repaglinide may be required.
Saxagliptin	Saxagliptin: AUC: ↑ 2.5-fold C_{max}: ↑ 1.6-fold Associated with a decrease in corresponding values for the active metabolite	Careful monitoring. Dose adjustment of saxagliptin may be required.
Tolbutamide	Tolbutamide: AUC: ↑ 1.7-fold	Careful monitoring. Dose adjustment of tolbutamide may be required.

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
Anti-infectives		
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 Clarithromycin	Telithromycine: AUC: ↑ 2-fold C_{max}: ↑1.5-fold Potential ↑in plasma concentrations of clarithromycin	Not recommended. Contraindicated in patients with severe renal impairment due to the risk of QT interval prolongation and serious hepatic adverse reactions (see section 4.3).
Isavuconazole	AUC: ↑ 5-fold C_{max}: ↑ 1.1 -fold	Not recommended due to increased risk of isavuconazole adverse reactions, please consult isavuconazole SmPC
Praziquantel	↑in plasma concentrations of praziquantel have been observed	Careful monitoring. Dose adjustment of praziquantel may be required.
Antimigraine Drugs		
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 reactions (see section 4.3).
Eletriptan	Eletriptan: AUC: ↑ 5.9-fold C_{max}: ↑ 2.7-fold	Not recommended.
Antineoplastics		
Irinotecan	Irinotecan: AUC: ↑ 2.1-fold	Contraindicated due to an alteration of the metabolism of this medicinal product (see section 4.3).
Sunitinib Dasatinib Lapatinib Nilotinib Erlotinib Dabrafenib Cabozantinib	Sunitinib AUC: ↑ 1.5-fold C_{max}: ↑ 1.5-fold Lapatinib: AUC: ↑ 3.6-fold Nilotinib: AUC: ↑ 3.0-fold Erlotinib: AUC: ↑ 1.9-fold C_{max}: ↑ 1.7-fold Dasatinib ↑in plasma concentrations of Dasatinib have been observed Dabrafenib AUC: ↑ 1.7-fold C_{max}: ↑ 1.3-fold Cabozantinib AUC: ↑ 1.4-fold C_{max}: ↔	Not recommended due to the risk of increased exposure to these medicinal products and QT prolongation.

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
Ibrutinib	Ibrutinib: AUC: ↑ 24-fold C_{max}: ↑ 29-fold	Not recommended as it may increase ibrutinib-related toxicity.
Crizotinib	Crizotinib AUC: ↑ 3.2-fold C_{max}: ↑ 1.4-fold	Not recommended due to the risk of QT interval prolongation and serious hepatic adverse reactions. Monitoring of QT-prolongation if used concomitantly.
Bortezomib Busulfan Docetaxel Imatinib Cabazitaxel	Bortezomib: AUC: ↑ 1.4-fold Imatinib: AUC: ↑ 1.4-fold C_{max}: ↑ 1.3-fold ↑in plasma concentrations of docetaxel have been observed Potential ↑in plasma concentrations of busulfan Cabazitaxel AUC: ↑ 1.3-fold	Careful monitoring. Dose adjustment of each medicinal product may be required.
Paclitaxel	Paclitaxel: No change in plasma concentration were shown with paclitaxel concentrate. No studies were performed with albumin bound nanoparticules.	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.
Antipsychotics, Anxiolytics and Hypnotics		
Triazolam Alprazolam Midazolam oral	AUC: ↑ have been observed C_{max}: ↑ have been observed	Contraindicated due to the risk of potentially prolonged or increased sedation and respiratory depression (see section 4.3).
Lurasidone	Lurasidone: AUC: ↑ 9-fold C_{max}: ↑ 6-fold	Contraindicated due to the increased risk of adverse reactions (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).
Sertindole	Potential ↑in plasma concentrations of sertindole.	Contraindicated due to the risk of QT prolongation (see section 4.3).
Quetiapine	Quetiapine: AUC: ↑ 6.2-fold C_{max}: ↑ 3.4-fold	Contraindicated as it may increase quetiapine-related toxicity (see section 4.3).
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.

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
Reboxetine	Reboxetine: AUC: ↑ 1.5-fold of both enantiomers	Not recommended because of reboxetine narrow's therapeutic margin.
Midazolam IV	Midazolam: AUC: ↑ 1.6-fold	Careful monitoring. Dose adjustment of midazolam IV may be required.
Buspirone	Potential ↑in plasma concentrations of buspirone.	Careful monitoring. Dose adjustement of buspirone may be required.
Aripiprazole	Aripiprazole AUC: ↑ 1.6-fold C_{max}: ↑ 1.4-fold	Careful monitoring. Aripiprazole dose should be reduced to approximatively one-half of its prescribed dose.
Risperidone	Potential ↑in AUC of risperidone:	Careful monitoring. Dose adjustment of risperidone may be required.
Antivirals products		
Saquinavir (saquinavir/ritonavir 1000/100 mg bid)	Saquinavir: AUC: ↔ C_{max}: ↔ Ketoconazole AUC: ↑ 2.7-fold C_{max}:↑ 1.5-fold (CYP3A4 enzyme inhibition by ritonavir)	Contraindicated due to the risk of QT prolongation (see section 4.3).
Paritaprevir/Ombitasvir (ritonavir)	Paritaprevir: AUC: ↑2.2-fold C_{max}: ↑1.7-fold Ombitasvir: AUC: ↑1.3-fold C_{max}: ↔ Ketoconazole: AUC: ↑2.1-fold C_{max}: ↑1.1-fold $t_{1/2}$: ↑ 4-fold	Contraindicated due to the increased risk of adverse reactions (see section 4.3).
Nevirapine	Ketoconazole: AUC: ↓0.28-fold C_{max}: ↓0.56-fold Nevirapine: plasma levels: ↑1.15-1.28-fold compared to historical controls (CYP3A enzyme induction)	Not recommended
Maraviroc	Maraviroc: AUC: ↑ 5-fold C_{max}: ↑ 3.4-fold	Careful monitoring. Maraviroc dose should be decreased to 150 mg twice daily.
Indinavir	Indinavir (600mg TID): AUC= 0.8-fold C_{min}: ↑ 1.3-fold (Relative to Indinavir 800 mg TID alone)	Careful monitoring. Dose reduction of indinavir to 600 mg every 8 hours should be considered.
Ritonavir	Ketoconazole: AUC: ↑3.4-fold C_{max}: ↑1.6-fold	A dose reduction of ketoconazole should be considered when co-administered with ritonavir dosed as

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
	(CYP3A enzyme inhibition)	an antiretroviral medicinal product or as a pharmacokinetic enhancer. (See also "Effects of other medicinal products on the metabolism of ketoconazole HRA ").
Beta Blockers		
Nadolol	↑in plasma concentrations of nadolol have been observed	Careful monitoring. Dose adjustment of nadolol may be required.
Calcium Channel Blockers		
Felodipine Nisoldipine	AUC: ↑ has been observed C_{max}: ↑ 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.
Cardiovascular Drugs, Miscellaneous		
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).
Bosentan	Bosentan: AUC: ↑ 2-fold C_{max}: ↑ 2-fold	Not recommended due to the potential for hepatic toxicity (see section 4.3).
Aliskiren	Aliskiren: AUC: ↑ 1.8-fold	Careful monitoring. Dose adjustment of aliskiren may be required.
Diuretics		
Eplerenone	Eplerenone: AUC: ↑ 5.5-fold	Contraindicated due to the increased risk of hyperkalaemia and hypotension (see section 4.3).
Gastrointestinal Drugs		
Aprepitant	Aprepitant: AUC: ↑ 5-fold	Careful monitoring. Dose adjustment of aprepitant may be required
Domperidone	Domperidone: AUC: ↑ 3.0 fold $C_{max:}$ ↑ 3.0 fold	Not recommended due to an increased risk in QT prolongation.
Naloxegol	Naloxegol AUC ↑ 12.9 fold C_{max} ↑ 9.6 fold	Not recommended
Immunosuppressants		
Everolimus Sirolimus (rapamycin)	Everolimus: AUC: ↑ 15.3-fold C_{max}: ↑ 4.1-fold Sirolimus (rapamycin): AUC: ↑ 10.9-fold C_{max}: ↑ 4.4-fold	Contraindicated due to the large increase in these medicinal products concentrations (see section 4.3).
Temsirolimus Tacrolimus Ciclosporine	Temsirolimus: AUC: ↔ C_{max}: ↔ Ciclesonide active metabolite: AUC: ↑ 3.5-fold	Not recommended unless necessary. Careful monitoring and dose adjustment of these medicinal products may be required.

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
Budesonide Ciclesonide	Rest of drugs ↑in plasma concentrations of these drugs have been observed	
Dexamethasone, fluticasone, methylprednisolone	Potential ↑in plasma concentrations of these drugs	Careful monitoring. Dose adjustment of these medicinal products may be required.
Lipid Lowering Drugs		
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).
Respiratory Drugs		
Salmeterol	Salmeterol AUC: ↑ 15-fold C_{max}: ↑ 1.4-fold	Not recommended due to an increased risk in QT prolongation.
Urological Drugs		
Fesoterodine Tolterodine Solifenacin	Fesoterodine active metabolite: AUC: ↑ 2.3-fold $C_{max:}$ ↑ 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).
Phosphodiesterase(PDE5) inhibitors		
Sildenafil Tadalafil Vardenafil	Tadalafil: AUC: ↑ 4-fold C_{max}: ↑ 1.2-fold Vardenafil: AUC: ↑ 10-fold C_{max}: ↑ 4-fold Potential ↑in plasma concentrations of sildenafil	Not recommended due to the increased risk of adverse reactions. Vardenafil is contraindicated in men older than 75 years old (see section 4.3).
Other		
Tolvaptan	↑in plasma concentrations of tolvaptan have been observed	Contraindicated due to an increase in the plasma concentrations (see section 4.3).
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).
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).
Cinacalcet	Cinacalcet AUC: ↑ 2 fold C_{max}: ↑ 2 fold	Careful monitoring. Dose adjustment of cinacalcet may be required.

Medicinal product by therapeutic area	Expected effect on drug levels	Recommendation for co-administration
Ebastine	↑in plasma concentrations of ebastine have been observed	Not recommended due to an increased risk in QT prolongation.

* Rosuvastatin is not a CYP 3A4 substrate. Ketoconazole did not produce any change in rosuvastatin pharmacokinetics, therefore, co-administration of ketoconazole 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.

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 and other steroidogenesis inhibitors (i.e. metyrapone).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of Ketoconazole HRA in pregnant women. Studies in animal have shown reproductive toxicity (see section 5.3). Preclinical data show that ketoconazole crosses the placenta and is teratogenic. Ketoconazole 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

Ketoconazole has a moderate influence on the ability to drive and 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 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 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
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia
Immune system disorders	Uncommon	Allergic conditions including anaphylactic shock, anaphylactoid reaction and anaphylactic reaction and angioedema
Endocrine disorders	Common	Adrenal insufficiency
Metabolism and nutrition disorders	Not known	Alcohol intolerance, anorexia, increased appetite
Psychiatric disorders	Not Known	Insomnia, nervousness
Nervous system disorders	Uncommon Not known	Headache, dizziness, somnolence Intracranial pressure increased (papilloedema, fontanelle bulging), paraesthesia
Eye disorders	Not known	Photophobia
Respiratory, thoracic and mediastinal disorders	Not known	Epistaxis
Gastrointestinal disorders	Common Not known	Nausea, abdominal pain, vomiting, diarrhoea Dyspepsia, flatulence, tongue discoloration, dry mouth, dysgeusia
Hepatobiliary disorders	Very common Rare	Liver function tests abnormal Serious hepatotoxicity, including jaundice, hepatitis, hepatic necrosis, hepatic cirrhosis, hepatic failure including cases necessitating transplantation or resulting in death.
Skin and subcutaneous tissue disorders	Common Uncommon Not known	Pruritus, rash Urticaria, alopecia Photosensitivity, erythema multiforme, dermatitis, erythema, , xeroderma

Musculoskeletal and connective tissue disorder	Not known	Myalgia, arthralgia
Reproductive system and breast disorders	Not known	Menstrual disorder, azoospermia, erectile dysfunction, gynaecomastia
General disorders and administration site conditions	Uncommon Very rare Not known	Asthenia Pyrexia Oedema peripheral, malaise, hot flush
Investigations	Very common Uncommon Not known	Hepatic enzyme increased Platelet count decreased 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 (≤ 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 initiation, should be taken into account before considering ketoconazole treatment. Ketoconazole should not be administered when liver enzymes are greater than 2 times the upper limit of normal or in association with other hepatotoxic medicinal products. 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 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 hepatoxicity. 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 1,200 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. The maximal dose that was used for treatment of Cushing's syndrome is 1,600 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 medicinal product 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: CORTICOSTEROIDS FOR SYSTEMIC USE, Anticorticosteroids, ATC code: H02CA03

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 17α-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 and safety

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 medicinal products, mainly with metyrapone, in patients with more severe disease or in those not completely responding to a single active substance or in those requiring a dose reduction of at least one of the medicinal products to improve tolerance. Ketoconazole has also been used with other therapies including surgery and pituitary radiation. Overall, ketoconazole was shown to be an effective medicinal product 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 Adrenocorticotropic Hormone (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 active substance 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 200 mg to 1,200 mg.

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 medicinal product. 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 has been performed. There are no data suggesting a need for a specific dose adjustment in this population.

In vitro data indicate that ketoconazole is a potent inhibitor of OATP1B1, OATP1B3, OAT3, OCT1 and OCT2 and to a lesser extent of OAT1 and BSEP. Inhibition of these different transporters at clinically relevant concentrations of ketoconazole cannot be excluded.

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 ketaconazole, 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 ^{3}H-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 60 tablets (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

HRA Pharma Rare Diseases
200 avenue de Paris
92320 CHATILLON
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/965/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2014
Date of latest renewal: 31 July 2019

10. DATE OF REVISION OF THE TEXT

01/2021

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/