ABBREVIATED PRESCRIBING INFORMATION (ROI & UK)

▼Ketoconazole HRA 200 mg tablets (ketoconazole).

Please refer to the Summary of Product Characteristics (SmPC) before prescribing Ketoconazole.

Presentation: Off-white to light cream, biconvex tablet. Each tablet contains 200mg ketoconazole. Also contains 19 mg of lactose (as monohydrate).

Indications: Treatment of endogenous Cushing's syndrome for adult and adolescent above 12 years of age.

Dosage: Prior to dosage refer to SmPC for full details. Requires supervision by a physician experienced in endocrinology or internal medicine. *Before starting treatment*-Liver function monitoring is mandatory. Liver enzymes should be monitored during treatment (see section 4.2 in the SmPC). Must not be initiated in patients with liver enzymes levels above 2 times the ULN (see section 4.3 in the SmPC). At treatment initiation, 24-hour urinary free cortisol should be controlled every few days/weeks. Initiation-recommended dose is 400-600mg/day, taken orally in two or three divided doses. Can be increased rapidly to 800-1200 mg/day, in two or three divided doses. *Daily dose* should be periodically adjusted. *Maintenance therapy*-administered in one of two ways: Block-only regimen or Block-and-Replace regimen. During treatment: close clinical follow-up required. Renal impairment: no specific dose adjustment recommendations. Hepatic impairment: contraindicated.

Contraindications: Hypersensitivity to ketoconazole and/or to any imidazole medication or excipients. Acute or chronic liver disease. Pregnant and breast-feeding women. Congenital or documented acquired QTc prolongation. Concomitant therapy with: CYP3A4 metabolised HMG-CoA reductase inhibitors, eplerenone, substances that may have their plasma concentrations increased and have QT prolonging potential, dabigatran, triazolam, oral midazolam, alprazolam, ergot alkaloids, lurasidone, quetiapine, telithromycin, clarithromycin, felodipine, nisoldipine, colchicine, irinotecan, everolimus, sirolimus (also known as rapamycin), vardenafil (in men >75yrs), paritaprevir/ombitasvir (ritonavir), fesoterodine, solifenacin and tolvaptan.

The list above is not an inclusive list of compounds that may interact with ketoconazole and result in potentially life-threatening reactions, please refer to SmPC before prescribing.

Special warnings and precautions: All patients should be monitored for liver and adrenal function/insufficiency. All patients need informing about signs/symptoms associated with hypocortisolism. Block-and-Replace regimen: teaching patients to adjust their glucocorticoid replacement therapy dose under conditions of stress. Patients should receive an emergency card and be equipped with an emergency glucocorticoid set. Monitoring of the effect on the QTc interval is advisable. ECG should be performed prior to the start of Ketoconazole HRA (within one week of starting treatment and as clinically indicated thereafter). In case of co-administration of an agent known to increase QTc interval, ECG monitoring is recommended. Contraception advice: Pregnancy prevention advice must be given. Decreased gastric acidity: advised to administer with acidic beverage. Potential for other medicinal products to affect ketoconazole: Ketoconazole HRA has a high potential for clinically important medicinal products interactions. CYP3A4 & CYP1A2 inducers: Consult the SmPC for concomitantly used products for recommendations regarding co-administration with strong CYP3A4 & CYP1A2 inhibitors. Inhibits Breast Cancer Resistance Protein (BCRP) and P-gp: consult SmPC. Use with naloxegol: not recommended. Use with hepatotoxic medicinal products: not recommended. Use with Pasireotide: not recommended. Coexisting inflammatory/autoimmune disorders: Supervision required for patients with Cushing's syndrome and coexisting inflammatory/autoimmune disorders. Avoid alcohol consumption. Patients with rare hereditary problems of galactase intolerance, Lapp lactase deficiency or glucose-galactose malabsorption must not take this medicine. **Interactions**:Oral anticoagulant medicines and certain medicines used to treat infections can interact, consult SmPC for full list of compounds that can interact with Ketoconazole (resulting in potentially life threatening adverse reactions). *In vitro* data indicate ketoconazole is a potent inhibitor of OATP1B1, OATP1B3, OAT3, OCT1 and OCT2 and to a lesser extent of OAT1 and BSEP: consult SmPC. **Fertility, pregnancy and lactation:** Contraindicated during pregnancy and breastfeeding.. Teratogenic potential was observed; animal data show effects on male and female reproduction.

Undesirable effects: Always consult the SmPC before prescribing.

Most commonly reported adverse reactions: adrenal insufficiency, nausea, vomiting, abdominal pain, diarrhoea, pruritus, rash and the hepatic enzymes increased. 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 frequently during treatment (see SmPC sections 4.2 and 4.4). Very common (≥ 1/10): Liver function tests abnormal, hepatic enzyme increased. Common (≥1/100 to <1/10): adrenal insufficiency, nausea, abdominal pain, vomiting, diarrhoea, pruritus, rash. Uncommon (≥1/1,000 to <1/100): Thrombocytopenia, allergic conditions (including anaphylactic shock, anaphylactoid reaction and anaphylactic reaction and angioedema), headache, dizziness, somnolence, urticaria, alopecia, asthenia, platelet count decreased. Rare (≥1/10,000 to <1/1,000): 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). Very rare (< 1/10,000): Pyrexia. Not known: cannot be estimated from the available data: Alcohol intolerance, anorexia, increased appetite, insomnia, nervousness, intracranial pressure increased (papilloedema, fontanelle bulging), paraesthesia, photophobia, epistaxis, dyspepsia, flatulence, tongue discoloration, dry mouth, dysgeusia, photosensitivity, erythema multiforme, dermatitis, erythema, xeroderma, myalgia, arthralgia, menstrual disorder, azoospermia, erectile dysfunction, gynaecomastia, oedema peripheral, malaise, hot flush, transient decrease of testosterone concentrations.

Basic NHS price in the UK: £480.00 for 60 tablets.

Marketing authorisation holder: HRA Pharma Rare Diseases, 200 avenue de Paris, 92320 Chatillon, France. Marketed in the UK and ROI by: HRA Pharma UK & Ireland Limited, Haines House, 21 John Street, Bloomsbury, London, WC1N 2BF. Additional information is available on request, contact medical information on 0800 917 9548 (UK) or email med.info.uk@hra-pharma.com (UK).

Marketing authorisation number: EU/1/14/965/001

Legal category: POM.

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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.
For the UK, reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
For ROI, Reporting forms and information can be found at www.hpra.ie. Adverse events should also be reported to HRA Pharma on 0800 917 9548 or email med.info.uk@hra-pharma.com