1.5.5.1 Professional information – clean copy

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27.10.2022 Approved by SAHPRA

PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

RANTRAL MR 10 (Tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains alfuzosin hydrochloride 10 mg in a modified release formulation.

Contains sugar: Lactose anhydrous 77 mg per tablet

3 PHARMACEUTICAL FORM

Tablets

White to off-white, uncoated, round, biconvex tablets debossed with 'RY 10' on one side of the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

RANTRAL MR 10 is indicated for the treatment of functional symptoms of benign prostatic hyperplasia.

Adjunctive therapy with urethral catheterisation for acute urinary retention (AUR) related to benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

Posology

Adults

Benign prostatic hyperplasia (BPH): The recommended dose for RANTRAL MR 10 is one tablet daily to be taken after meals as bioavailability in the fasting state is less than in the fed state.

Acute urinary retention (AUR): One 10 mg tablet daily after a meal to be taken from the first day of catheterisation.

Special populations

Elderly population

Elderly, treated hypertensive patients and renal insufficiency

RANTRAL MR 10 is not indicated in these patient populations as a 5 mg dosage form is not available.

Paediatric population

Efficacy and safety of RANTRAL MR 10 in children less than 18 years has not been established. RANTRAL MR 10 is contraindicated in children (see section 4.3).

Method of administration

Tablet should be swallowed whole. See section 4.4.

4.3 Contraindications

RANTRAL MR 10 is contra-indicated in:

- hypersensitivity to alfuzosin or any of the ingredients in the medicine
- orthostatic hypotension
- combination with other alpha$_1$-adrenoceptor blockers
- hepatic insufficiency
- severe renal insufficiency
- children
- pregnancy and lactation

4.4 Special warnings and precautions for use

In some subjects, in particular patients receiving antihypertensive medications, postural hypotension with or without symptoms (dizziness, fatigue, sweating) may develop within a few hours following administration. In such cases, the patient should lie down until the symptoms have completely disappeared. These effects are usually transient, occur at the beginning of treatment and do not usually prevent the continuation of treatment. The patient should be warned of the possible occurrence of such events.

In coronary patients, RANTRAL MR 10 (alfuzosin hydrochloride) should not be prescribed alone.

In patients with coronary artery disease and ischaemic heart disease/angina pectoris, the specific treatment for coronary insufficiency should be continued.
If angina pectoris reappears or gets worse, RANTRAL MR 10 should be discontinued.
Patients with a known hypersensitivity to alpha$_1$-adrenoceptor blockers should be closely monitored.

Intraoperative Floppy Iris Syndrome (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with some alpha1-blockers (including RANTRAL 10 MR).
Although the risk of this event with RANTRAL 10 MR appears very low, ophthalmic surgeons should be informed in advance of cataract surgery of current or past use of alpha1-blockers, as IFIS may lead to increased procedural complications

Tablet should be swallowed whole. Any other mode of administration, such as crunching, crushing, chewing, grinding or pounding to powder should be prohibited. These actions may lead to inappropriate release and absorption of the drug and therefore possible early adverse reactions.

As with all alpha1-receptor blockers, RANTRAL 10 MR should be used with caution in patients with acute cardiac failure.

Concomitant use of RANTRAL 10 MR and potent CYP3A4 inhibitors (such as itraconazole, ketoconazole, protease inhibitors, clarithromycin, telithromycin and nefazodone) should be avoided (see section 4.5). RANTRAL 10 MR should not be used concomitantly with CYP3A4 inhibitors that are known to increase the QTc interval (e.g. itraconazole and clarithromycin) and a temporary interruption of RANTRAL 10 MR treatment is recommended if treatment with such medicine is initiated.

Prolonged erections and priapism have been reported with alpha-1 blockers including alfuzosin in post marketing experience. If priapism is not treated immediately, it could result in penile tissue damage and permanent loss of potency, therefore the patient should seek immediate medical assistance (see section 4.8).

RANTRAL MR 10 contains lactose as an inactive ingredient. Patients with a rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take RANTRAL MR 10**.**

4.5 Interaction with other medicines and other forms of interaction

Concomitant use with alpha$_1$-adrenoceptor blockers may result in hypotension (see section 4.3).

Combinations to be taken into account:

- Antihypertensive medicines (section 4.4).
- Nitrates
- General anaesthetics: Administration of general anaesthetics to a patient treated with RANTRAL MR 10 may lead to decrease in blood pressure.
- Potent CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir since RANTRAL MR 10 blood levels are increased.

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation have not been established.

4.7 Effects on ability to drive and use machines

There are no data available on the effect of driving vehicles. As side-effects such as vertigo, dizziness and asthenia may occur, these should be taken into account when driving vehicles and operating machinery.

4.8 Undesirable effects

b) Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse event
Nervous system disorders	Frequent: Less frequent:	Faintness, vertigo, dizziness and headache Drowsiness, malaise and syncope
Eye disorders	Unknown Frequency	Intraoperative Floppy Iris Syndrome (IFIS) Vision abnormal
Cardiac disorders	Less frequent Unknown Frequency	Symptomatic hypotension (postural), tachycardia, palpitations, oedema, flushes and chest pain (See section 4.4). Syncope, angina pectoris in patients with pre-existing coronary artery disease Atrial fibrillation
Vascular disorders	Less frequent	Hypotension (postural) Flushing
Blood and lymphatic system disorders	Unknown Frequency	Neutropenia Thrombocytopenia
Respiratory, thoracic and mediastinal disorders	Less frequent	Rhinitis
Gastro-intestinal	Frequent	Nausea, gastralgia, abdominal pain and diarrhoea

system disorders	Less frequent	Dry mouth, vomiting
Hepato-biliary disorders	Unknown Frequency	Hepatocellular injury, cholestatic liver disease
Skin and subcutaneous tissue disorders	Less frequent:	Dry mouth, rash, pruritus, urticaria, angioedema
Reproductive system and breast disorders	Unknown Frequency	Priapism
General disorders	Less frequent	Asthenia, malaise, flushes, oedema, chest pain

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In case of overdosage, the patient should be hospitalised, kept in the supine position and conventional treatment of hypotension should take place.

RANTRAL 10 MR is not easily dialysable because of its high degree of protein binding. Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

PHARMACOLOGICAL CLASSIFICATION

A 5.2 Adrenolytics (sympatholytics). Pharmacotherapeutic group: alpha-adrenoreceptor antagonists. ATC code: G04CA01

5.1 Pharmacodynamic properties

Alfuzosin hydrochloride is an orally active quinazoline derivative.

It is a selective peripherally acting antagonist of post-synaptic alpha$_1$-adrenoreceptors.

Reported *In vitro* pharmacological studies have documented the selectivity of alfuzosin hydrochloride for the alpha1-adrenoceptors located in the prostate, bladder base and prostatic urethra.

Alpha$_1$-adrenoreceptors blockade decreases infra-vesical obstruction via a direct action on prostatic smooth muscle.

Reported *In vivo* animal studies have shown that alfuzosin hydrochloride decreases urethral pressure and therefore, resistance to urine flow during micturition. Moreover, alfuzosin hydrochloride inhibits the hypertonic response of the urethra more readily than that of vascular muscle, and shows functional uroselectivity in experimental animals.

In man, alfuzosin hydrochloride improves voiding parameters by reducing urethral tone and bladder outlet resistance and facilitates bladder emptying.

In addition, alfuzosin significantly increases the success rate of spontaneous voiding after catheter removal in men with an episode of acute urinary retention (AUR) related to benign prostatic hyperplasia (BPH).

5.2 Pharmacokinetics properties

Alfuzosin hydrochloride is absorbed with a mean absolute bioavailability of 64 %.

RANTRAL MR 10 tablets are bioequivalent to the innovator under fed and fasting conditions in healthy, adult, male subjects. Under fed conditions, RANTRAL MR 10 tablets have a mean C_{max} of 15,4 ng/ml and a T_{max} of 7 hours. The half-life is 8,5 hours. The AUC_t and $AUC_{-\infty}$ are 232,8 and 235,1 ng.hr/ml respectively. Under fasting conditions, RANTRAL MR 10 tablets have a mean C_{max} of 9,2 ng/ml and a T_{max} of 5,2 hours. The elimination half-life is 11,2 hours. The AUC_t and $AUC_{-\infty}$ are 172,2 and 181,5 ng.hr/ml respectively.

Maximum blood levels and bioavailability are affected by food intake.

Compared to middle aged volunteers, the pharmacokinetic parameters (C_{max} and AUC) are not increased in elderly patients.

Compared to subjects with normal renal function, mean C_{max} and AUC values were about 5 % and 7 % increased in patients with mild to moderate renal impairment, without modification of the apparent elimination half-life. There are no data available on severe renal impairment.

The binding of alfuzosin hydrochloride to total proteins is about 90 %.

Alfuzosin hydrochloride undergoes extensive metabolism by the liver, with only 11 % of the parent compound being excreted as the unchanged product in the urine.

The majority of the metabolites, which are inactive, are excreted in the faeces (75 % to 91 %).

It is reported that in subjects aged over 75 years, absorption of alfuzosin hydrochloride is more rapid and the peak levels are higher. Bioavailability may be increased and in some patients the volume of distribution is reduced. The elimination half-life remains unchanged.

The volume of distribution and clearance of alfuzosin hydrochloride are increased in renal insufficiency, with or without dialysis, owing to an increase in the free fraction.
In patients with severe hepatic insufficiency, the elimination half-life of alfuzosin hydrochloride is prolonged. A two-fold increase in C_{max} values and a three–fold increase in the AUC is observed. Bioavailability is increased in comparison with that in healthy volunteers.

The pharmacokinetic profile of alfuzosin hydrochloride is not affected by chronic cardiac insufficiency.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Lactose monohydrate
- Povidone
- Colloidal anhydrous silica Ph.Eur
- Purified talc
- Magnesium stearate Ph.Eur
- Hypromellose
- Hydroxypropyl cellulose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

Store at or below 25 °C in the original container, protected from moisture.

KEEP OUT OF REACH OF CHILDREN.

6.4 Special precautions for storage

Protect from moisture. Keep blister in carton until required for use.

6.5 Nature and contents of container

Ten tablets are packed in clear, transparent, Aclar laminated PVC and aluminium foil blister strips. Cartons contain 30 or 60 tablets.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

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Roodepoort, 1724

South Africa

8 REGISTRATION NUMBER

A40/5.2/0392

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1. Last approval: November 2010

10 DATE OF REVISION OF THE TEXT

27 October 2022