# PROFESSIONAL INFORMATION

## SCHEDULING STATUS S2

## PROPRIETARY NAME AND DOSAGE FORM

Rizagran® OTC (orodispersible tablets)

## COMPOSITION

**Active ingredient:**

Each RIZAGRAN OTC orodispersible tablet contains 7,267 mg of rizatriptan benzoate equivalent to 5 mg of rizatriptan.

**Inactive ingredients:**

Aspartame, calcium silicate (FM 1 000), crospovidone (Polyplasdone XL) Type A, magnesium stearate, mannitol (Pearlitol SD 200), silica colloidal anhydrous (Aerosil 200), silicified microcrystalline cellulose (Prosolv SMCC50), sweet orange flavour.

Each RIZAGRAN OTC orodispersible tablet contains sugar alcohol (mannitol 35,373 mg).

Each RIZAGRAN OTC orodispersible tablet contains an artificial sweetener (aspartame 2,800 mg).

## PHARMACOLOGICAL CLASSIFICATION

A 7.3 Migraine preparations

## PHARMACOLOGICAL ACTION

**Pharmacodynamic properties:**

Rizatriptan is an orally active serotonergic agonist that has been shown in radioligand binding assays and functional pharmacological bioassays to act selectively at 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors. Rizatriptan has no clinically significant activity at 5-$HT_2$ or 5-$HT_3$ receptor subtypes, nor at alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

Rizatriptan acts at craniovascular 5-$HT_{1B}$ receptors to cause selective constriction of the extracerebral, intracranial arteries that are thought to be dilated during a migraine attack. In anaesthetised dogs, rizatriptan reduces carotid artery blood flow selectively and has much lesser effects on blood flow in the coronary and pulmonary artery vasculature.

Rizatriptan also inhibits cranial sensory pathways, by acting at peripheral and central inhibitory 5-$HT_{1D}$ receptors that are present in animals and humans on trigeminal nerves. When stimulated, these trigeminal nerves release peptides (e.g., substance P, calcitonin gene related peptide and neurokinin A), that can produce vasodilation and inflammation around blood vessels in sensitive tissues and which relay nociceptive information into the central nervous system. In animals, activation of trigeminal 5-$HT_{1D}$ receptors by rizatriptan prevents the release of these peptides, leading to decreased dilation of sensitive blood vessels, decreased inflammation in the dura mater and reduced central pain transmission.
Rizatriptan has only weak partial agonist constrictor effects on human isolated coronary artery segments *in vitro*. This finding is consistent with its lack of activity at 5-$HT_{2A}$ receptors, which are known to mediate contraction in these blood vessels.

**Pharmacokinetic properties:**

***Absorption:***

Rizatriptan is well absorbed following oral administration. The mean oral bioavailability of the tablet is approximately 40 to 45 % and mean peak plasma concentrations ($C_{max}$) are reached in approximately 1 to 1,5 hours ($T_{max}$). Administration of an oral tablet dose with a high-fat breakfast had no effect on the extent of rizatriptan absorption, but absorption was slightly delayed.

The bioavailability and $C_{max}$ of an orally disintegrating dosage form is similar to that following tablet administration. The apparent rate of absorption is somewhat slower, with $T_{max}$ averaging 1,6 to 2,5 hours.

***Distribution:***

Rizatriptan is minimally bound (14 %) to plasma proteins. The volume of distribution is approximately 140 litres in male patients, and 110 litres in female patients.

***Metabolism:***

The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not pharmacologically active. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-$HT_{1B/1D}$ receptor, is formed to a minor degree, but does not contribute significantly to the pharmacodynamic activity of rizatriptan. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14 % of those of parent compound, and it is eliminated at a similar rate. Other minor metabolites include the N-oxide, the 6-hydroxy compound, and the sulfate conjugate of the 6-hydroxy metabolite. None of these minor metabolites are pharmacologically active. Following oral administration of $^{14}$C-labelled rizatriptan, rizatriptan accounts for about 17 % of circulating plasma radioactivity.

***Cytochrome P450 isoforms:***

Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 isoforms 3A4/5, IA2, 2C9, 2C19, or 2E1; however, rizatriptan is a competitive inhibitor (Ki =1 400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

***Elimination:***

The plasma half-life of rizatriptan in males and females averages 2 to 3 hours. The plasma clearance of rizatriptan averages about 1 000 to 1 500 ml/min in males and about 900 to 1 100 ml/min in females; about 20 to 30 % of this is renal clearance. Following an oral dose of $^{14}$C-labelled rizatriptan, about 80 % of the radioactivity is excreted in urine, and about 10 % of the dose is excreted in faeces. This shows that the metabolites are excreted primarily via the kidneys.

After oral doses of 2,5 to 10 mg, the pharmacokinetics of rizatriptan are nearly linear. Consistent with its first-pass metabolism, approximately 14 % of an oral dose is excreted in urine as unchanged rizatriptan while 51 % is excreted as indole acetic acid metabolite.

When rizatriptan 10 mg was administered every 2 hours for three doses on four consecutive days, the plasma concentrations of rizatriptan increased within each day, consistent with its half-life, but no plasma accumulation of rizatriptan occurred from day to day.

***Special populations:***

*Gender:*

The AUC of rizatriptan (10 mg orally) was about 25 % lower in males as compared to females, $C_{max}$ was 11 % lower, and $T_{max}$ occurred at approximately the same time. This apparent pharmacokinetic difference was of no clinical significance.

*Elderly:*

The plasma concentrations of rizatriptan observed in elderly subjects (age range 65 to 77 years) were similar to those observed in the young.

*Hepatic impairment:*

Following oral administration in patients with hepatic impairment caused by mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of rizatriptan were similar to those seen in young male and female subjects.

*Renal impairment:*

In patients with renal impairment (creatinine clearance 10 to 60 ml/min/1,73 $m^2$), the AUC of rizatriptan was not significantly different from that in healthy subjects. In haemodialysis patients, the AUC for rizatriptan was approximately 44 % greater than that in patients with normal renal function. The maximal

plasma concentration of rizatriptan in patients with all degrees of renal impairment was similar to that in healthy subjects.

**INDICATIONS**

RIZAGRAN OTC is indicated for the acute relief of migraine attacks, with or without aura, in patients previously diagnosed by a medical practitioner and initiated on treatment with rizatriptan.

**CONTRAINDICATIONS**

**RIZAGRAN OTC is contraindicated in patients with:**

- Hypersensitivity to rizatriptan or any of the excipients of RIZAGRAN OTC (see “COMPOSITION”).
- Concurrent administration of monoamine oxidase (MAO) inhibitors or within 2 weeks of discontinuation of MAO inhibitor therapy (see “INTERACTIONS”).
- Concurrent administration with linezolid.

**Based on the mechanism of action of the medicine class, 5-$HT_{1B/1D}$ agonists, RIZAGRAN OTC is also contraindicated in patients with:**

- Uncontrolled hypertension.
- Established coronary artery disease, including ischaemic heart disease (angina pectoris, history of myocardial infarction, stroke or documented silent ischaemia), signs and symptoms of ischaemic heart disease, or Prinzmetal’s angina.
- RIZAGRAN OTC is contraindicated in patients with severe hepatic or severe renal insufficiency.
- Concomitant use of rizatriptan, as in RIZAGRAN OTC and ergotamine, ergot derivatives (including methysergide), or other 5-$HT_{1B/1D}$ agonists (see “WARNINGS AND SPECIAL PRECAUTIONS”).
- RIZAGRAN OTC is contraindicated in patients with a previous cerebrovascular accident (CVA) or transient ischaemic attach (TIA).
- RIZAGRAN OTC is contraindicated in peripheral vascular disease.
- Safety has not been established in pregnancy and lactation (see “PREGNANCY AND LACTATION”).

- RIZAGRAN OTC is not recommended for use in paediatric patients under 18 years of age.

**WARNINGS AND SPECIAL PRECAUTIONS**

- For warnings and special precautions related to the use of RIZAGRAN OTC together with other medicines, refer to “INTERACTIONS.”
- RIZAGRAN OTC should only be administered to patients in whom a clear diagnosis of migraine has been established. RIZAGRAN OTC should not be administered to patients with basilar or hemiplegic migraine.
- RIZAGRAN OTC should not be used to treat “atypical” headaches, i.e., those that might be associated with potentially serious medical conditions (e.g., stroke, ruptured aneurysm) in which cerebrovascular vasoconstriction could be harmful.
- There have been reports of serious coronary events with the class of 5-$HT_{1B/1D}$ agonists including RIZAGRAN OTC (see “SIDE EFFECTS”). Prior to prescribing RIZAGRAN OTC, cardiovascular assessment should be considered in patients at risk for coronary artery disease (CAD) [e.g., patients with hypertension, diabetics, smokers, and those with strong family history for CAD]. Those, in whom CAD is established, should not be given RIZAGRAN OTC (see “CONTRAINDICATIONS”).
- Angioedema (e.g., facial oedema, tongue swelling and pharyngeal oedema) may occur in patients treated with triptans, including RIZAGRAN OTC. If angioedema of the tongue or pharynx occurs, the patient should be placed under medical supervision until symptoms have resolved. Treatment should promptly be discontinued and replaced by an agent belonging to another class of medicines.

**Medication overuse headache (MOH):**

Prolonged use of any painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained, and treatment should be discontinued. The diagnosis of MOH should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

**Warnings related to excipients:**

- Phenylketonuric patients should be informed that RIZAGRAN OTC orodispersible tablets contain aspartame, a source of phenylalanine which may be harmful for people with phenylketonuria. RIZAGRAN OTC should therefore not be used in patients with phenylketonuria.
- RIZAGRAN OTC contains mannitol and may have a laxative effect.

**Effects on ability to drive and use machines:**

Migraine or treatment with RIZAGRAN OTC may cause somnolence in some patients. Dizziness has also been reported in some patients receiving rizatriptan. Patients should, therefore, evaluate their ability to perform complex tasks during migraine attacks and after administration of RIZAGRAN OTC.

**INTERACTIONS**

**Pharmacokinetic interactions:**

Pharmacokinetic interaction studies were carried out with the MAO-A inhibitor, moclobemide; the selective serotonin reuptake inhibitor (SSRI), paroxetine; propranolol and two other beta-blockers, nadolol and metoprolol; and oral contraceptives. Significant interactions were seen with the MAO-A inhibitor and propranolol.

**Monoamine oxidase inhibitors:**

Rizatriptan is principally metabolised via monoamine oxidase, 'A' subtype (MAO-A). Plasma concentrations of rizatriptan and its active N-monodesmethyl metabolite were increased by concomitant administration of a selective, reversible MAO-A inhibitor. Similar or greater effects are expected with nonselective, irreversible MAO inhibitors or linezolid. Administration of RIZAGRAN OTC to patients taking inhibitors of MAO is contraindicated (see "CONTRAINDICATIONS").

**Selective Serotonin Reuptake Inhibitors/ Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome:**

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs) or Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and

triptans as in RIZAGRAN OTC. If concomitant treatment with RIZAGRAN OTC and an SSRI (e.g. sertraline, escitalopram oxalate and fluoxetine) or SNRI (e.g. venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

**Other 5-$HT_{1B/1D}$ agonists:**

RIZAGRAN OTC should not be used concomitantly with other 5-$HT_{1B/1D}$ agonists (e.g. sumatriptan).

**Ergot derivatives:**

Concomitant administration of RIZAGRAN OTC and ergotamine-type medicines (e.g., ergotamine, dihydro-ergotamine or methysergide) within 6 hours of each other is not recommended, as additive vasospastic effects may occur.

**St John's wort:**

Undesirable effects may be more common during concomitant use of RIZAGRAN OTC (5-$HT_{1B/1D}$ agonists) and herbal preparations containing St John's wort (*Hypericum perforatum*).

**Beta blockers:**

Plasma concentrations of rizatriptan may be increased by concomitant administration of propranolol. This increase is most probably due to first-pass metabolic interaction between the two medicines, since MAO-A plays a role in the metabolism of both rizatriptan and propranolol. In patients receiving propranolol, the 5 mg dose of RIZAGRAN OTC should be used (see "DOSAGE AND DIRECTIONS FOR USE"). No pharmacokinetic interaction was observed between rizatriptan and the beta blockers nadolol or metoprolol. Based on *in vitro* data, no pharmacokinetic interaction is expected with timolol or atenolol.

**CYP2D6 substrates:**

*In vitro* studies indicate that rizatriptan inhibits cytochrome P450 2D6 (CYP2D6). Clinical interaction data are not available. The potential for interaction should be considered when RIZAGRAN OTC is administered to patients taking CYP2D6 substrates.

**PREGNANCY AND LACTATION**

RIZAGRAN OTC tablets are contraindicated in pregnancy and lactation.

Safety has not been established in pregnancy or lactation.

**Fertility:**

Effects on human fertility have not been investigated. Animal studies only revealed minimal effect on fertility at plasma concentrations far in excess of human therapeutic concentrations (more than 500-fold).

**DOSAGE AND DIRECTIONS FOR USE**

RIZAGRAN OTC orodispersible tablets may be taken as an alternative to the oral tablet, at the same recommended dosage. Administration with liquid is not necessary.

The tablet should be placed on the tongue, where it will dissolve and be swallowed with the saliva. The orodispersible tablets can be used in situations in which liquids are not available, or to avoid the nausea and vomiting that may accompany the ingestion of tablets with liquids.

**Adults 18 years of age and older:**

The recommended dose is 5 to 10 mg. Clinical experience has shown that a 10 mg dose provides the optimal clinical benefit, but some patients do respond to lower doses.

Onset of relief (i.e., reduction of headache) can occur within 30 minutes after dosing.

**Re-dosing:**

Doses should be separated by at least 2 hours; no more than 30 mg (6 tablets of 5 mg) should be taken in any 24-hour period.

- ***For headache recurrence within 24 hours*:** If headache returns after relief of the initial attack, further doses may be taken. The above dosing limits should be observed.
- ***After non-response:*** The effectiveness of a second dose for treatment of the same attack, when an initial dose is ineffective has not been examined in controlled trials.

Clinical studies have shown that patients who do not respond to treatment of an attack are still likely to respond to treatment for subsequent attacks.

Although less effective than 10 mg, a 5 mg dose is also available. This dose may be appropriate for some patients e.g., those receiving propranolol.

**Patients receiving propranolol:**

In patients receiving propranolol, the 5 mg dose of RIZAGRAN OTC should be used, up to a maximum of 3 doses in any 24-hour period (see “PHARMACOLOGICAL ACTION” and “INTERACTIONS”).

**SIDE EFFECTS**

The most common side effects of RIZAGRAN OTC are dizziness, somnolence, and asthenia/fatigue.

**Nervous system:**

***Frequent:*** Paraesthesia, headache, hypoaesthesia, decreased mental acuity, dizziness, and somnolence.

***Less frequent:*** Ataxia, vertigo, syncope, tremor and dysgeusia.

***Frequency not known:*** Seizure, serotonin syndrome.

**Psychiatric disorders:**

***Frequent:*** Insomnia.

***Less frequent:*** Disorientation, nervousness.

**Eye disorders:**

***Less frequent:*** Blurred vision.

**Cardiac disorders:**

***Frequent:*** Palpitation.

***Less frequent***: Arrhythmia, ECG abnormalities, tachycardia.

***Frequency not known:*** Dysrhythmia, bradycardia, myocardial ischaemia/infarction, cerebrovascular accident.

**Vascular disorders:**

***Less frequent:*** Hot flushes, hypertension, cerebrovascular accident.

***Frequency not known:*** Peripheral vascular ischaemia.

**Respiratory, thoracic, and mediastinal disorders:**

***Frequent:*** Pharyngeal discomfort.

***Less frequent:*** Dyspnoea, wheezing.

**Gastrointestinal disorders:**

***Frequent:*** Nausea, dry mouth, vomiting, diarrhoea, dyspepsia.

***Less frequent:*** Thirst.

***Frequency not known:*** Ischaemic colitis.

**Skin and subcutaneous tissue disorders:**

***Frequent:*** Flushing.

***Less frequent:*** Pruritus, urticaria, angioedema (e.g., facial oedema, tongue swelling, pharyngeal oedema), rash, sweating.

***Frequency not known*:** Toxic epidermal necrosis.

**Musculoskeletal, connective tissue and bone disorders:**

***Frequent:*** Regional heaviness, neck pain, stiffness.

***Less frequent:*** Regional tightness, muscle weakness, facial pain.

***Frequency not known:*** Myalgia.

**Immune system disorders:**

***Frequency not known*:** Hypersensitivity, anaphylaxis, angioedema.

**General disorders and administration site conditions:**

***Frequent:*** Pain in the abdomen or chest, fatigue/asthenia.

**Investigations*:***

***Frequency not known:*** ECG abnormalities.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**

Hypertension, vomiting, dizziness, incontinence, bradycardia, syncope, AV block or other serious cardiovascular symptoms could occur after overdosage.

**Gastrointestinal decontamination:**

Activated charcoal should be considered in patients suspected of an overdose with RIZAGRAN OTC. Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed. Treatment is symptomatic and supportive.

The effects of haemo- or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

**IDENTIFICATION**

White to grey-white, round, flat tablet, debossed with “RZT” on one side, and “5” on the other side.

**PRESENTATION**

Al/Al blisters or Al/Al peel-off blisters.

RIZAGRAN OTC orodispersible tablets are packed in a carton with an enclosed leaflet.

Pack size: 2 orodispersible tablets.

**STORAGE INSTRUCTIONS**

Store at or below 25 ºC.

Keep blister strips in the outer carton until required for use.

Do not remove the tablets from the blister strips until required for use to protect from moisture.

**REGISTRATION NUMBER**

45/7.3/0237

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION**

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[1]Company Reg. No: 1990/001979/07