PROFESSIONAL INFORMATION FOR ZYRAMIG ODT

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ZYRAMIG ODT 5 mg

(Rizatriptan benzoate 5 mg orally disintegrating tablets)

ZYRAMIG ODT 10 mg

(Rizatriptan benzoate 10 mg orally disintegrating tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **ZYRAMIG ODT 5 mg** tablet contains 7.265 mg of Rizatriptan benzoate equivalent to 5 mg Rizatriptan.

Each **ZYRAMIG ODT 10 mg** tablet contains 14.53 mg of Rizatriptan benzoate equivalent to 10 mg Rizatriptan.

Excipients with known effect

ZYRAMIG ODT 5 mg contains sweetener (Aspartame 1.5 mg).

ZYRAMIG ODT 10 mg contains sweetener (Aspartame 3 mg).

ZYRAMIG ODT 5 mg contains sugar alcohol (Manitol 25 mg).

ZYRAMIG ODT 10 mg contains sugar alcohol (Manitol 50 mg).

Excipients:

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Orally Disintegrating Tablets, 5 and 10 mg

ZYRAMIG ODT 5 mg:

White to off-white round shaped uncoated tablets debossed with L58 on one side and plain on the other side.

ZYRAMIG ODT 10 mg:

White to off-white round shaped uncoated tablets debossed with L59 on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZYRAMIG ODT is indicated for the acute treatment of migraine attacks with or without aura in adults.

4.2 Posology and method of administration

Posology

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 pain to mild or none) can occur within 30 minutes after dosing.

Redosing in adults:

Doses should be separated by at least 2 hours; no more than 30 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, is not known.

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

Adult patients receiving propranolol

In patients receiving propranolol, the 5 mg dose of **ZYRAMIG ODT** should be used up to a maximum of 3 doses in any 24 hour period.

Special Populations

Use in Children (Under 18 years of age):

Efficacy of Rizatriptan in paediatric patients under 18 years of age has not been established.

Therefore, its use in this age group is not recommended.

Method of administration

Oral.

The orodispersible tablet should be removed from the packaging with dry hands just prior to dosing and placed on the tongue, where it will dissolve and be swallowed with the saliva.

4.3 Contraindications

ZYRAMIG ODT is contra-indicated in patients with:

- hypersensitivity to rizatriptan or any of the ingredients of **ZYRAMIG ODT** listed in section 5.1.
- concurrent administration of monoamine oxidase (MAO) inhibitors (including linezolid), or use within 2 weeks of discontinuation of MAO inhibitor therapy. (see Sections 4.4, 4.5 and 5.1).

ZYRAMIG ODT is contraindicated in patients with severe hepatic or severe renal insufficiency.

Concomitant use of rizatriptan and ergotamine, ergot derivatives (including methysergde), or other 5-$HT_{1B/1D}$ receptor agonists (see section 4.5)

Based on the mechanism of action of this class of compounds, **ZYRAMIG ODT** is also contra-indicated in patients with:

- uncontrolled hypertension
- established coronary artery disease, including ischaemic heart disease (angina pectoris, history at myocardial infarction or documented silent ischaemia). signs and symptoms of ischaemic heart disease or Prinzmetal's angina
- **ZYRAMIG ODT** is contraindicated in pregnancy and lactation (see Section 4.6)
- History of stroke or transient ischaemic attack (TIA)

Peripheral vascular disease, including (but not limited to) ischaemic bowel disease

- **ZYRAMIG ODT** is not recommended for use in paediatric patients under 18 years of age.

4.4 Special warnings and precautions for use

ZYRAMIG ODT should only be administered to patients in whom a clear diagnosis of migraine has been established. **ZYRAMIG ODT** should not be administered to patients with basilar or hemiplegic migraine.

ZYRAMIG ODT 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.

Rizatriptan can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat (see section 4.8). Where such symptoms are thought to indicate ischaemic heart disease, no further dose should be taken and appropriate evaluation should be carried out.

There have been reports of serious coronary events with this class of medicines including **ZYRAMIG ODT**. Prior to prescribing this medicine, 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 **ZYRAMIG ODT** (see Section 4.3).

Other 5-$HT_{1B/1D}$ agonist (e.g. sumatriptan) should not be used concomitantly with **ZYRAMIG ODT**.

Administration of ergotamine-type medications (e.g. ergotamine, dihydroergotamine or methysergide) and **ZYRAMIG ODT** within 6 hours of each other is not recommended.

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans including **ZYRAMIG ODT**. If concomitant treatment with **ZYRAMIG ODT** 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 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) (see Section 4.5).

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 adult patients receiving propranolol, a 5-mg dose of rizatriptan should be used (see Section 4.2).

Overuse of acute migraine medicines such as tryptans (including **ZYRAMIG ODT**), for 10 or more days per month, may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraines attacks. Detoxification of patients, including withdrawal of the overused medicines, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be

necessary.

Angioedema (e.g. facial oedema, tongue swelling and pharyngeal oedema) may occur in patients treated with triptans, among which is rizatriptan. 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 drugs.

Use in the elderly

The pharmacokinetics of rizatriptan was similar in elderly (aged older than or 65 years) and in younger adults.

Phenylketonuria

Each 5 mg tablet contains 1.5 mg and 10 mg tablet contains 3 mg of aspartame.

Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

4.5 Interaction with other medicines and other forms of interaction

Ergotamine, ergot derivatives (including methysergide), other 5-HT$_{1B/1D}$ receptor agonists:

Due to an additive effect, the concomitant use of rizatriptan and ergotamine, ergot derivatives (including methysergide), or other 5-HT$_{1B/1D}$ receptor agonists (e.g. sumatriptan, zolmitriptan, naratriptan) increase the risk of coronary artery vasoconstriction and hypertensive effects. This combination is contra-indicated (see section 4.3).

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 MAO-A inhibitor including linezolid. Administration of **ZYRAMIG** to patients taking inhibitors of MAO is contra-indicated (see Section 4.3 & 4.4).

Beta-Blockers:

Plasma concentrations of rizatriptan may be increased by concomitant administration of propranolol. In adult patients receiving propranolol, the 5 mg dose of rizatriptan should be used (see Section 4.2). 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.

Selective Serotonin Reuptake Inhibitors / Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome (see Section 4.4).

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 (see Section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

ZYRAMIG ODT is contraindicated in pregnancy (see section 4.3)

Breastfeeding

ZYRAMIG ODT is contraindicated in women who are breastfeeding (see section 4.3)

Fertility

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

4.7 Effects on ability to drive and use machines

Migraine or treatment with **ZYRAMIG ODT** may cause somnolence in some patients. Dizziness, ataxia, disorientation, blurred vision and vertigo have has also been reported in some patients receiving **ZYRAMIG ODT**. Patients should, therefore, evaluate their ability to perform complex tasks during migraine attacks and after administration of **ZYRAMIG ODT**

4.8 Undesirable effects

Summary of the reported safety profile

The most frequent adverse reactions include dizziness, somnolence, asthenia/fatigue.

Tabulated summary of adverse events

System organ class	Frequency	Undesirable effect

Immune system disorders	Less frequent	angioedema (e.g. facial oedema, tongue swelling, pharyngeal oedema)
	Frequency unknown	Hypersensitivity reaction, anaphylaxis / anaphylactoid reaction
Psychiatric disorders	Frequent	Insomnia,
	Less frequent	Disorientation, nervousness
Nervous system disorders	Frequent	Paraesthesia, headache, hypoaesthesia, decreased mental acuity, Dizziness, somnolence
	Less frequent	Ataxia, vertigo, dysgeusia / bad taste, tremor, Syncope
	Frequency unknown	Seizure, serotonin syndrome
Eye disorders	Less frequent	Blurred vision
Cardiac disorders	Frequent	Palpitation, tachycardia
	Frequency unknown	Myocardial ischaemia or infarction[1], bradycardia, dysrhythmia, cerebrovascular accident
Vascular disorders	Frequent	Hot flushes/flashes
	Less frequent	Hypertension
	Frequency unknown	Peripheral vascular ischaemia
Respiratory, thoracic and mediastinal disorders	Frequent	Pharyngeal discomfort, dyspnoea
	Less frequent	Wheezing
Gastrointestinal disorders	Frequent	Nausea, dry mouth, vomiting, diarrhoea
	Less frequent	Thirst, dyspepsia
	Frequency unknown	Ischaemic colitis
Skin and	Frequent	Flushing, sweating
	Less frequent	Pruritus, urticarial, rash

subcutaneous tissue disorders	Frequency unknown	toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Frequent	Regional heaviness (pain, pressure, discomfort, or a strange feeling/sensation in the back, neck, jaw, upper belly or in the shoulders or arms)
	Less frequent	Neck pain, regional tightness, stiffness, muscle weakness, facial pain, myalgia
General disorders and administration site conditions	Frequent	Pain in the abdomen or chest Asthenia/fatigue
Investigations	Frequency unknown	ECG abnormalities

[1]. Most of these adverse reactions have been reported in patients with risk factors predictive of coronary artery disease.

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

No overdose of rizatriptan were reported during clinical trials in adults.

Dizziness and somnolence were the most common **ZYRAMIG ODT** related adverse effects.

Vomiting, incontinence, bradycardia and complete heart block have been reported.

Hypertension and syncope have been reported. Treatment should be symptomatic and supportive.

Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.3 Vascular Medicines; Migraine Preparations.

Pharmacotherapeutic group: antimigraine preparations, selective serotonin (5HT1) agonists

ATC code: N02CC04

Rizatriptan is a 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-HT2 or 5-HT3 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.

Rizatriptan also inhibits cranial sensory pathways, by acting at peripheral and central inhibitory 5-HT_{1D} receptors. 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.

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.

In a study in healthy male subjects, rizatriptan 10 produced slight, transient peripheral vasoconstriction (measured as a 5,1 mmHg increase in toe-arm systolic blood pressure gradient). In contrast, intravenous ergotamine (0,25 mg) produced a 14,6 mmHg increase in toe-arm systolic blood pressure gradient. When ergotamine and rizatriptan were given together, the increase in toe-arm systolic blood pressure gradient was similar to that when ergotamine was given alone.

Electrocardiographic effects of two 10 mg doses of rizatriptan, separated by 2 hours, were studied in 157 migraine patients (age range 18 to 72 years) during a migraine attack. No evidence of myocardial ischemia was observed, as defined by standard ECG criteria. No clinically relevant ECG effects were observed.

In a study in healthy male subjects, the effects of rizatriptan, 10 and 15 mg, in a battery of tests of sympathetic reflexes were investigated in comparison to placebo and the sympatholytic medicine, clonidine. No effects of rizatriptan on sympathetic reflexes were demonstrated.

5.2 Pharmacokinetic properties

Absorption

Rizatriptan is completely absorbed following oral administration. The mean oral bioavailability of the tablet is approximately 40 - 45 %, and mean peak plasma concentrations (C_{max}) are reached in approximately 1 - 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. In clinical trials rizatriptan was administered without regard to food. The bioavailability and C_{max} of rizatriptan ODT are similar to that following tablet administration. The apparent rate of absorption is somewhat slower, with rizatriptan.

In a pharmacokinetic study in adults, median T_{max} was 0,67 hours for the 10 mg tablet and 1,33 hours for the **ZYRAMIG ODT 10 mg**.

Distribution

Rizatriptan is minimally bound (14 %) to plasma proteins. The volume of distribution is approximately 140 litres in male subjects, and 110 litres in female subjects. Studies in rats indicate that rizatriptan crosses the blood-brain barrier to a limited extent.

Biotransformation

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 $5HT_{1B/1D}$ receptor, is formed to a minor degree, but does not contribute significantly to the pharmacodynamic activity of rizatriptan. Plasma concentrations of Nmonodesmethyl- 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 is pharmacologically active. Following oral administration of 14C- labelled rizatriptan,

rizatriptan accounts for about 17 % of circulating plasma radioactivity.

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 (see Section 4.5).

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 =1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

Elimination

The plasma half-life of rizatriptan in males and females averages 2-3 hours. The pharmacokinetics of rizatriptan are linear in males and nearly linear in females following intravenous doses ≤60 mcg/kg. The plasma clearance of rizatriptan averages about 1000- 1500 ml/min in males and about 900-1100 ml/min in females; about 20-30 % of this is renal clearance. Following an oral dose of 14C-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 ~~R~~r̲izatriptan was administered every 2 hours for three doses on four consecutive days, the plasma concentrations of rizatriptan increased within each day, consistent with its t½, but no plasma accumulation of rizatriptan occurred from day to day.

Characteristics in patients

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 patients (above 65 years):

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 – 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.

5.3 Preclinical safety data

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains 1,5 mg and 3 mg Aspartame respectively in the 5 mg and 10 mg ODT

carboxymethyl cellulose calcium, colloidal silicon dioxide, magnesium stearate, mannitol, microcrystalline cellulose, peppermint Flavour (501500 TP0504) containing maltodextrin, modified corn starch and natural flavours.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister pack: 60 months from the date of manufacture.

HDPE container pack: 24 months from the date of manufacture.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep the blisters in the carton until required for use.

Keep HDPE containers tightly closed.

Store in the original package in order to protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Blister Pack:

1. Tablets are packed in blister pack of cold form laminate, 25 µ OPA/45µ aluminum foil/60 µ PVC as forming material and plain 30 µ aluminium foil (6-8) gsm HSL as lidding material, packed in pre-printed carton
2. Tablets are packed in blister pack clear film PVC/PE/PVdC, 250/25/90 gsm PVdC as forming material and plain 25 µ aluminium foil (6-8) gsm HSL as lidding material, packed in a plain triple laminated pouch:

Peelable blister Pack:

Tablets are packed in blister pack of cold form laminate, 25 µ OPA/45µ aluminium foil/60µ PVC as forming material and child resistant peelable 50 gsm paper/ 12 µ PET/ 20 µ aluminium foil 7 gsm heat seal lacquer as lidding material, packed in pre-printed carton

Pack size: 2's, 3's, 5's, 6's, 10's, 18's, 20's, 100's

HDPE Container Pack:

Tablets are packed in 40 cc, round white HDPE container with 33-400 neck finish closed with a white 33 mm child resistant with pulp and heat seal liner and packed in outer carton. Each HDPE container contains 2 sachets of 1 g silica gel.

Pack size: 30's tablets.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Ground Floor, Block 1,

Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock Ext 12,

Alberton, Gauteng

8. REGISTRATION NUMBERS

5 mg : 47/7.3/2001

10 mg: 47/7.3/0110

9. DATE OF FIRST AUTHORISATION

04 October 2022

10. DATE OF REVISION OF THE TEXT

07 February 2025

PM0249_01

Vanita Rajool

Digitally signed by Vanita Rajool
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