APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MICRANIA MELTS 5 mg orodispersible tablets.

MICRANIA MELTS 10 mg orodispersible tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MICRANIA MELTS 5 mg: Each orodispersible tablet contains 7,265 mg rizatriptan benzoate, equivalent 5 mg rizatriptan.

MICRANIA MELTS 10 mg: Each orodispersible tablet contains 14,53 mg rizatriptan benzoate, equivalent 10 mg rizatriptan.

MICRANIA MELTS is sugar free.

MICRANIA MELTS 5 mg: Each tablet contains aspartame 1,450 mg.

MICRANIA MELTS 10 mg: Each tablet contains aspartame 2,90 mg.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Orodispersible tablets

MICRANIA MELTS 5 mg: White, round, biconvex tablets.

MICRANIA MELTS 10 mg: White, round, biconvex tablets with score line on one side. The score line on the 10 mg tablets is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults:

The recommended dose in adults is 5 mg or 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:

Patients receiving propranolol should take MICRANIA MELTS 5 mg, up to a maximum of 3 x MICRANIA MELTS 5 mg doses in a 24-hour period (see sections 4.5 and 5.2).

Paediatric population

The safety and efficacy of MICRANIA MELTS 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

MICRANIA MELTS need not be taken with liquid.

Patients should be instructed not to remove the tablet from the blister until just prior to dosing. The tablet should be removed from the blister with dry hands and the tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

4.3 Contraindications

- Hypersensitivity to rizatriptan or to any of the ingredients of MICRANIA MELTS
- 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 5.2)
- Uncontrolled hypertension
- Established coronary artery disease, including ischaemic heart disease (angina pectoris, history of myocardial infarction or documented silent ischaemia), signs and symptoms of ischaemic heart disease or Prinzmetal's angina
- Previous cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- Peripheral vascular disease, including (but not limited to) ischaemic bowel disease
- Concomitant use of MICRANIA MELTS with ergotamine, ergot derivatives (including methysergide) and 5-$HT_{1B/1D}$ agonists (see section 4.5)
- Severe hepatic or renal insufficiency
- Pregnancy and lactation (see section 4.6)
- Paediatric patients under the age of 18 years as the safety and efficacy have not been established.

4.4 Special warnings and precautions for use

Rizatriptan, as in MICRANIA MELTS, is principally metabolised via monoamine oxidase. Plasma concentrations of rizatriptan and its active N-monodesmethyl metabolite were

increased by concomitant administration of a MAO inhibitor including linezolid. Administration of MICRANIA MELTS to patients taking inhibitors of MAO is contraindicated (see sections 4.3 and 4.5).

Transient (slight) increases in blood pressure (approximately 2-3 mmHg), deemed to be not significant, have been observed in healthy patients who have received maximal doses of MICRANIA MELTS (10 mg every 2 hours for three doses). During long-term monitoring of migraine patients in controlled studies, no consistent effects on blood pressure or heart rate were observed.

At an oral dose of 40 mg, rizatriptan did not alter regional cerebral blood flow or middle cerebral artery blood velocity in healthy male subjects.

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

MICRANIA MELTS 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.

MICRANIA MELTS 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 MICRANIA MELTS (see section 4.8). Prior to prescribing MICRANIA MELTS, 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].

Patients in whom CAD is established should not be given MICRANIA MELTS (see section 4.3).

5-$HT_{1B/1D}$ receptor agonists have been associated with coronary vasospasm. In rare cases, myocardial ischaemia or infarction have been reported with 5-HT1B/1D receptor agonists including MICRANIA MELTS (see section 4.8).

Other 5-$HT_{1B/1D}$ agonists (e.g., sumatriptan) should not be used concomitantly with MICRANIA MELTS.

Administration of ergotamine-type medications (e.g., ergotamine, dihydro-ergotamine or methysergide) and MICRANIA MELTS within 6 hours of each other is not recommended. Although additive vasospastic effects were not observed during studies in which 16 healthy males received oral rizatriptan and parenteral ergotamine, additive vasospastic effects are theoretically possible.

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 MICRANIA MELTS. If concomitant treatment

with MICRANIA MELTS and an SSRI (e.g., sertraline, citalopram, escitalopram, 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) (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, the 5-mg dose of MICRANIA MELTS should be used (see section 4.2).

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

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

The potential for interaction should be considered when MICRANIA MELTS is administered to patients taking CYP2D6 substrates (see section 4.5).

Overuse of acute migraine medicines such as triptans (including MICRANIA MELTS), 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.

Use in the elderly

The pharmacokinetics of rizatriptan were similar in elderly (aged ≥ 65 years) and in younger adults. In clinical trials, there were no apparent differences in efficacy or in overall adverse experience rates between patients under 65 years of age and those 65 and above (n= 17).

Aspartame

MICRANIA MELTS contains aspartame, which is metabolised to phenylalanine, and may be hazardous to patients with phenylketonuria

4.5 Interaction with other medicines and other forms of interaction

Ergotamine, ergot derivatives (including methysergide) and 5-$HT_{1B/1D}$ 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.

Administration of ergotamine-type medications (e.g. ergotamine, dihydro-ergotamine or methysergide) and MICRANIA MELTS, is contraindicated (see section 4.3).

Monoamine oxidase inhibitors:

Rizatriptan, as contained in MICRANIA MELTS is principally metabolised via MAO. Plasma concentrations of rizatriptan and its active N-monodesmethyl metabolite are increased by concomitant administration of reversible MAO inhibitors, including linezolid. Due to a risk of coronary artery vasoconstriction and hypertensive episodes administration of MICRANIA MELTS to patients taking inhibitors of MAO is contraindicated (see section 4.3).

Beta-blockers:

Plasma concentrations of rizatriptan, as contained in MICRANIA MELTS may be increased by concomitant administration of propanolol. This increase is most probably due to first-pass metabolic interaction between the two medicines, since MAO plays a role in the metabolism of both rizatriptan and propranolol. This interaction leads to a mean increase in AUC and Cmax of 70-80 %. In patients receiving propranolol, MICRANIA MELTS 5 mg should be used (see section 4.2). No pharmacokinetic interaction was observed between MICRANIA MELTS 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 (SSRIs) /Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and Serotonin Syndrome:

Cases of life-threatening serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and tryptans (see section 4.4).

CYP 2D6 substrates:

In vitro studies indicate that rizatriptan, as in MICRANIA MELTS, inhibits cytochrome P450 2D6 (CYP 2D6). Clinical interaction data are not available. The potential for interaction should be considered when MICRANIA MELTS is administered to patients taking CYP 2D6 substrates.

4.6 Fertility, pregnancy and lactation

The safety and efficacy of MICRANIA MELTS in pregnancy and lactation have not been established and is therefore contraindicated (see section 4.3).

4.7 Effects on ability to drive and use machines

Migraine or treatment with MICRANIA MELTS may cause somnolence in some patients. Dizziness, ataxia, disorientation, blurred vision and vertigo have also been reported in some patients receiving MICRANIA MELTS. Patients should, therefore, evaluate their

ability to perform complex tasks during migraine attacks and after administration of MICRANIA MELTS.

4.8 Undesirable effects

a) Summary of the safety profile

The most common side effects reported in clinical studies were dizziness, somnolence, and asthenia/fatigue.

b) Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Immune system disorders	Less frequent	Hypersensitivity reaction*, anaphylaxis /anaphylactoid reaction*
Psychiatric disorders	Frequent Less frequent	Insomnia Disorientation, nervousness
Nervous system disorders	Frequent Less frequent Frequency unknown	Dizziness, somnolence, headache, paraesthesia, decreased mental acuity, hypoesthesia Ataxia, vertigo, syncope, dysgeusia/bad taste*, Serotonin syndrome*, seizure*
Eye disorders	Less frequent	Blurred vision
Cardiac disorders	Frequent	Palpitation, tachycardia

	Less frequent Frequency unknown	Cerebrovascular accident*, bradycardia* Myocardial ischaemia or infarction*, dysrhythmia*, ECG abnormalities*
Vascular disorders	Frequent Less frequent Frequency unknown	Hot flushes/flashes Hypertension Peripheral vascular ischaemia*
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Pharyngeal discomfort, dyspnoea Wheezing*
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Nausea, vomiting, dry mouth, diarrhoea Dyspepsia, thirst Ischaemic colitis*
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Sweating, flushing Pruritus, urticaria*, angioedema* (e.g. facial oedema, tongue swelling, pharyngeal oedema), rash* Toxic epidermal necrolysis*
Musculoskeletal, connective tissue and bone 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 administrative site conditions	Frequent	Pain in abdomen or chest, asthenia/fatigue

*Post-marketing experience.

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found on SAHPRA's website: www.sahpra.org.za under "online services".

4.9 OVERDOSE

Signs and symptoms:

No overdoses of MICRANIA MELTS were reported during clinical trials in adults.

Dizziness and somnolence were the most common MICRANIA MELTS related adverse effects.

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

Hypertension and syncope have been reported.

Management of overdose:

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

Pharmacotherapeutic group: Antimigraine preparations, selective serotonin (5HT1) agonist

ATC code: N02C C04

Pharmacological classification: A 7.3 Vascular Medicines; Migraine Preparations.

Mechanism of action

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 and has little or no effect or pharmacological activity at 5-HT_2, 5-HT_3; adrenergic $alpha_1$, $alpha_2$ or beta; D_1, D_2, dopaminergic, histaminic H_1; muscarinic; or benzodiazepine 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.

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 mg 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 mg 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 Cmax of MICRANIA MELTS orodispersible tablets are similar to that following tablet administration. The apparent rate of absorption is somewhat slower, with MICRANIA MELTS orodispersible tablets. In a pharmacokinetic study in adults, median T_{max} was 0,67 hours for the 10 mg tablet and 1,33 hours for the 10 mg MICRANIA MELTS orodispersible tablets.

Effect of Food: The absorption of rizatriptan, as in MICRANIA MELTS is delayed by approximately 1 hour when administered together with food. Therefore, onset of effect may be delayed when MICRANIA MELTS is administered in the fed state.

Distribution:

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

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 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 sulphate conjugate of the 6-hydroxy metabolite. None of these minor metabolites is pharmacologically active. Following oral administration of ^{14}C-labeled 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 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 1 000 - 1 500 mL/min in males and about 900 – 1 100 mL/min in females; about 20 – 30 % of this is renal clearance. Following an oral dose of ^{14}C-labeled rizatriptan, about 80 % of the radioactivity is excreted in urine, and about 10 % of the dose is excreted in faeces. Metabolites are therefore primarily excreted 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. No more than 1 % is excreted in urine as the active N-monodesmethyl metabolite.

When rizatriptan is administered every 2 hours for three doses on four consecutive days, the plasma concentrations of rizatriptan increase within each day, consistent with its half-life, but no plasma accumulation of the active ingredient occurs from day to day.

Pharmacokinetics in special patient groups:

Gender:

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

Elderly:

The plasma concentrations of rizatriptan observed in elderly subjects (age range 65 to 77 years) are 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 are similar to those seen in young male and female patients.

Renal impairment:

In patients with renal impairment (creatinine clearance 10 – 60 mL/min/1,73 m^2), the AUC of rizatriptan is not significantly different from that in healthy patients. In haemodialysis patients, the AUC for rizatriptan is 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 is similar to that in healthy subjects.

Paediatric population

Rizatriptan is contraindicated in children 18 years and below.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame

Magnesium stearate

Maize starch

Microcrystalline cellulose

Mint powder

Silica colloidal anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not to remove the tablet from the blister until just prior to dosing.

Keep blister in carton until required for use.

6.5 Nature and contents of container

Aluminium foil blister strip containing either 3 or 6 tablets packed in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

MICRANIA MELTS 5 mg*: A51/7.3/0561

MICRANIA MELTS 10 mg: A51/7.3/0562

*Not all strengths may be marketed

9. DATE OF FIRST AUTHORISATION

March 2022

10. DATE OF REVISION OF THE TEXT

March 2022