PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF MEDICINE
Mederizan 5 (Orodispersible Tablets)
Mederizan 10 (Orodispersible Tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Mederizan 5
Each orodispersible tablet contains 7,265 mg of rizatriptan benzoate equivalent to 5 mg of rizatriptan.
Mederizan 10
Each orodispersible tablet contains 14,53 mg of rizatriptan benzoate equivalent to 10 mg of rizatriptan.
Sugar free
Excipient with known effect:
Mederizan 5
Each orodispersible tablet contains 1,45 mg of aspartame.
Mederizan 10
Each orodispersible tablet contains 2,90 mg of aspartame.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Orodispersible tablets.

Mederizan 5
White, round, biconvex tablets, with dimensions 7,1 ± 0,1 mm and 2,4 ± 0,2 mm in thickness.
Mederizan 10
White, round, biconvex tablets, with a score line one side and dimensions 10,0 ± 0,1 mm and 2,9 ± 0,2 mm in thickness. The score line is not intended for breaking the orodispersible tablet.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Mederizan 10 is indicated for the acute treatment of migraine attacks with or without aura in adults.

4.2 Posology and method of administration
Posology
Recommended dosing in adults
The recommended dose in adults is 5 - 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 Mederizan 10 should be used, up to a maximum of 3 doses in any 24-hour period (see section 5.1 and 4.5).

Paediatric population
Children and adolescents (under 18 years of age)
Efficacy of rizatriptan in paediatric patients under 18 years of age has not been established. Therefore, the use of Mederizan 10 in this age group is not recommended.

Method of administration
Oral route.
Mederizan 10 orodispersible tablets need not be taken with liquid. Patients should be instructed not to remove the blister from the outer packaging until just prior to dosing. The blister pack should be opened with dry hands and the orodispersible tablet should be placed on the tongue, where it will dissolve and be swallowed with saliva.

4.3 Contraindications
Mederizan 10 is contraindicated in:
- hypersensitivity to rizatriptan or to any of the excipients listed in section 6.1.
- concurrent administration of monoamine oxidase (MAO) inhibitors including linezolid or use within 2 weeks of discontinuation of MAO inhibitor therapy.
- uncontrolled hypertension, moderately severe to severe hypertension or untreated mild 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.
- pregnancy and lactation (see section 4.6).
- children and adolescents under 18 years of age.
- history of previous cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- peripheral vascular disease, including (but not limited to) ischaemic bowel disease.
- concomitant use of rizatriptan and ergotamine, ergot derivatives (including methysergide), or other 5-$HT_{1B/1D}$ receptor agonists (see section 4.5).

4.4 Special warnings and precautions for use
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 Mederizan 10 to patients taking inhibitors of MAO is contraindicated (see sections 4.3 and 4.5).

In healthy young male and female subjects who received maximal doses of rizatriptan (10 mg every 2 hours for three doses), transient increases in blood pressure (approximately 2-3 mmHg) were observed. 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.

Mederizan 10 should only be administered to patients in whom a clear diagnosis of migraine has been established. Mederizan 10 should not be administered to patients with basilar or hemiplegic migraine.

Mederizan 10 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 Mederizan 10 (see section 4.8). Prior to prescribing Mederizan 10, cardiovascular assessment should be considered in patients at risk for coronary artery disease (CAD). Patients in whom CAD is established should not be given Mederizan 10 (see section 4.3).
5-$HT_{1B/1D}$ receptor agonists have been associated with coronary vasospasm. In cases, myocardial ischaemia or infarction have been reported with 5-$HT_{1B/1D}$ receptor agonists.

Other 5-$HT_{1B/1D}$ agonists (e.g., sumatriptan) should not be used concomitantly with Mederizan 10.

Administration of ergotamine-type medications (e.g., ergotamine, dihydro-ergotamine or methysergide) and Mederizan 10 within 6 hours of each other is not recommended.
At least 24 hours should elapse after the administration of an ergotamine-containing preparation before rizatriptan as in Mederizan 10 is given. Although additive vasospastic effects were not observed in a clinical pharmacology study in which 16 healthy males received oral rizatriptan and parenteral ergotamine, such additive effects are theoretically possible (see section 4.3).

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 rizatriptan as in Mederizan 10. If concomitant treatment with Mederizan 10 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 Mederizan 10 should be used (see sections 4.2 and 4.5).

Overuse of acute migraine medicines such as triptans (including Mederizan 10), 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 medicines.

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*).
The potential for interaction should be considered when rizatriptan is administered to patients taking CYP 2D6 substrates (see section 4.5).

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.

Excipients:
Mederizan 10 contains aspartame, a source of phenylalanine which may be harmful to people with phenylketonuria (PKU), a rare inherited disorder that causes an amino acid (phenylalanine) to build up in the body.

4.5 Interaction with other medicines and other forms of interaction
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 Mederizan 10 to patients taking inhibitors of MAO is contraindicated (see sections 4.3 and 4.4).

Beta-blockers
Plasma concentrations of rizatriptan may be increased by concomitant administration of propranolol. This interaction leads to a mean increase in AUC and C_{max} of 70-80 %. In adult patients receiving propranolol, the 5 mg dose of Mederizan 10 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.
In a drug interaction study, nadolol and metoprolol did not alter plasma concentrations of rizatriptan.

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 (see section 4.4).

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 concomitant combination is contraindicated (see section 4.3).

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

4.6 Fertility, pregnancy and lactation
Mederizan 10 is contraindicated in pregnant women or women who are breastfeeding their infants (see section 4.3).

4.7 Effects on ability to drive and use machines
Migraine or treatment with Mederizan 10 may cause somnolence in some patients. Dizziness, ataxia, disorientation, blurred vision and vertigo have had also been reported in some patients receiving Mederizan 10. Patients should, therefore, evaluate their ability to perform complex tasks during migraine attacks and after administration of Mederizan 10.

4.8 Undesirable effects
a. **Tabulated summary of adverse reactions**

System Organ Class	Frequency	Undesirable effect
Immune system disorders	*Less frequent*	Hypersensitivity reaction, anaphylaxis / anaphylactoid reaction.
Psychiatric disorders	*Frequent*	Insomnia.
	Less Frequent	Disorientation, nervousness.
Nervous system disorders	*Frequent*	Paraesthesia, headache, hypoaesthesia, decreased mental acuity, tremor, dizziness, somnolence.
	Less frequent	Ataxia, disorientation, insomnia, vertigo, syncope, dysgeusia/bad taste.
	Frequency unknown	Seizure, serotonin syndrome.
Eye disorders	*Less frequent*	Blurred vision.
Cardiac disorders	*Frequent*	Palpitation, tachycardia.
	Less frequent	Dysrhythmia, ECG abnormalities, tachycardia, cerebrovascular accident, bradycardia.
	Frequency unknown	Myocardial ischaemia or infarction.
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	Ischemic colitis.
Skin and subcutaneous tissue disorders	*Frequent*	Flushing, sweating.
	Less frequent	Pruritus, urticaria, angioedema (e.g., facial oedema, tongue swelling, pharyngeal oedema), rash.
	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 abdomen or chest, asthenia/fatigue.

c. 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 " Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose
No overdoses of rizatriptan were reported during clinical trials in adults.

Dizziness and somnolence were the most common Mederizan 10 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
Pharmacotherapeutic group: antimigraine preparations, selective serotonin (5HT1) agonists, 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.
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, 10 mg rizatriptan 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 orodispersible tablets are similar to that following tablet administration. The apparent rate of absorption is somewhat slower, with rizatriptan 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 rizatriptan orodispersible tablets.

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.

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 is pharmacologically active. Following oral administration of ^{14}C- 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 (K_i=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 ^{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 was administered every 2 hours for three doses on four consecutive days, the plasma concentrations of rizatriptan increased within each day, consistent with its $t_{½}$, 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 - 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.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Microcrystalline cellulose
Maize starch
Silica colloidal anhydrous
Aspartame (E951)
Mint powder consisting of:
- mint oil
- terpeneless mint oil
- eucalyptol
- menthone
- isomenthone
- methyl acetate
- menthol

Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 30 °C.
The patient should be instructed not to remove the blister from the outer packaging until the patient is ready to consume the orodispersible tablet.
KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container
PA/AL/PVC-Aluminium blisters.
Pack sizes available in 2, 3, 6, 12 or 18 orodispersible tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDERS OF CERTIFICATE OF REGISTRATION
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