

NEW ZEALAND DATA SHEET

RIZAMELT

Rizatriptan benzoate orodispersible tablets 5mg & 10mg



Presentation

The 5 mg RIZAMELT orodispersible tablet is a white to off-white coloured, round, flat faced bevelled edged tablet, debossed with "M" on one side and "RN1" on the other side.

The 10 mg RIZAMELT orodispersible tablet is a white to off-white coloured, round, flat faced bevelled edged tablet, debossed with "M" on one side and "RN2" on the other side.

Not all pack types or strengths may be marketed.

Therapeutic Class

Rizatriptan is an anti migraine agent, which is a selective 5-hydroxytryptamine_{1B/1D} (5-HT_{1B/1D}) receptor agonist.

Indications

RIZAMELT is indicated for the acute treatment of migraine attacks with or without aura.

Dosage and Administration

Clinical experience has shown that the 10 mg rizatriptan benzoate dose provides the optimal clinical benefit. Onset of relief (i.e., reduction of headache pain to mild or none) can occur within 30 minutes after dosing.

Redosing

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, 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.

Patients Receiving Propranolol

In patients receiving propranolol, a 5 mg dose of rizatriptan should be used, up to a maximum of 3 doses in any 24-hour period (see **Interactions** and **Pharmacokinetics - Metabolism**).

Patients receiving propranolol should not take RIZAMELT 10 mg orodispersible tablets.

Administration

The orodispersible tablets are packaged in blister strips within an outer aluminium sachet (pouch). Patients should be instructed not to remove the tablet from the blister until just prior to dosing.

The blister pack should be peeled open with dry hands and the orodispersible tablet placed on the tongue, where it will dissolve and be swallowed with the saliva. Administration with liquid is not necessary.

Contraindications

RIZAMELT is contraindicated in patients with:

- hypersensitivity to rizatriptan or any of the ingredients
- concurrent administration of monoamine oxidase inhibitors (MAOIs), or use within 2 weeks of discontinuation of MAOI therapy (see **Interactions** and **Pharmacokinetics - Metabolism**).

Based on the mechanism of action of this class of compounds, RIZAMELT is also contraindicated in patients with:

- 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.
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Warnings and Precautions

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

RIZAMELT 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.

Patients at Risk for Coronary Artery Disease

There have been rare reports of serious coronary events with this class of medicines including rizatriptan (see **Adverse Effects**). Prior to prescribing this medicine, cardiovascular assessment should be considered in patients at risk for coronary artery disease (CAD) [e.g., patients with hypertension or diabetes, smokers, and those with strong family history for CAD]. Those in whom CAD is established should not be given RIZAMELT (see **Contraindications**).

Other 5-HT_{1B/1D} Agonists

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

Ergotamine-Type Medications

Administration of ergotamine-type medications (e.g., ergotamine, dihydro-ergotamine or methysergide) and RIZAMELT within 6 hours of each other is not recommended. 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.

Serotonin Syndrome

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. If concomitant treatment with RIZAMELT 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) (see **Interactions**).

Pregnancy

There are no clinical studies of rizatriptan in pregnant women. No treatment-related foetal effects or malformations were observed in developmental and reproductive toxicity studies conducted in rats and rabbits; nor were adverse effects detected in any reproductive parameters during early or late gestation, or during the lactation period. High maternal medicine exposure, high foetal tissue exposure, and high milk exposure were achieved in these studies. Because animal reproductive and developmental toxicity studies are not always predictive of human response, RIZAMELT should be used during pregnancy only if clearly needed.

Lactation

Rizatriptan is excreted in the milk of lactating rats; however, no data exist in humans.

Paediatric Use

Safety and effectiveness of rizatriptan in paediatric patients have not been established; therefore, RIZAMELT is not recommended for use in paediatric patients under 18 years of age.

Use in the Elderly

The pharmacokinetics of rizatriptan were similar in elderly (aged ≥ 65 years) and in younger adults. Because migraine occurs infrequently in the elderly, clinical experience with rizatriptan is limited in such patients. 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 ($n = 17$).

Animal Toxicology

Acute Toxicity

The approximate oral LD₅₀ of rizatriptan was 700 mg/kg and 2227 mg/kg in mice and rats, respectively. The approximate intravenous LD₅₀ values were 89 and 141 mg/kg in mice and rats, respectively.

Chronic Toxicity

The toxicity potential of rizatriptan was evaluated in a series of repeat dose oral toxicity studies up to one year in dogs and rats and up to 14 weeks in mice. There were no adverse findings that would preclude administration of RIZAMELT at the recommended therapeutic dosages to humans.

Carcinogenesis

The carcinogenic potential of rizatriptan was evaluated in a 106-week study in rats and a 100-week study in mice at oral doses of up to 125 mg/kg/day (625-fold the human dose of 10 mg or 0.2 mg/kg). These doses produced exposure margins (AUC ratios) of up to 600- and 400-fold in rats and mice, respectively, over the human systemic exposure at a therapeutic dose of 10 mg (0.2 mg/kg). For both rats and mice, no evidence of carcinogenicity was seen with increasing doses of rizatriptan.

Mutagenesis

Rizatriptan, with and without metabolic activation, was neither genotoxic, mutagenic, nor clastogenic in all *in vitro* and *in vivo* genetic toxicity studies, including: microbial mutagenesis, *in vitro* chromosome aberration assays, *in vitro* V-79 mammalian cell mutagenesis assays, an *in vitro* alkaline elution/rat hepatocyte assay, and an *in vivo* chromosome aberration assay in mouse bone marrow.

Reproduction

No adverse effects on fertility or reproductive performance, and no foetal toxicity or malformations were observed in female and male rats (except slightly decreased body weight at the high dose) given oral doses of rizatriptan up to 100 and 250 mg/kg/day, respectively (500 and 1250-fold the human dose of 10 mg or 0.2 mg/kg). In addition, no adverse effects on reproductive parameters were detected during early or late gestation, or during the lactation period.

These doses provided exposure margins more than 900-fold over the human systemic exposure, based on the AUC ratio derived from rat maternal medicine levels compared to humans treated with 10 mg (0.2 mg/kg). High placental transfer occurred, as evidenced by rat foetal plasma levels of 20 to 40% of the

maternal plasma levels. High milk transfer occurred, and resulted in rat milk levels that were 5-fold, or greater, the maternal plasma levels.

Although high maternal, foetal and neonatal exposure to rizatriptan occurred in these studies, no adverse treatment-related effects were observed on F1 survival, development, behaviour, reproductive performance, or testicular histology, nor were there any effects seen in the F2 offspring. In an additional developmental study in rats, a slight increase in pup mortality and slight decreases in weight gain and performance in a passive avoidance test were observed at a dose of 100 mg/kg/day or greater.

No adverse effects on development, and no foetal toxicity or malformations were observed in pregnant rabbits (except slightly decreased body weight at the high dose) given oral doses of rizatriptan up to 50 mg/kg/day (250-fold the human dose of 10 mg or 0.2 mg/kg). These doses produced high maternal medicine levels, resulting in a 475-fold exposure margin, based on the AUC ratio derived from rabbit maternal medicine levels compared to humans treated with 10 mg (0.2 mg/kg). High placental transfer occurred with rabbit foetal tissue levels reaching 42 to 49% of the maternal plasma levels.

Development

There were no adverse effects on foetal development in rats or rabbits exposed to large multiples of the human therapeutic dose of rizatriptan during early and late gestation. High placental transfer of rizatriptan was documented by foetal plasma and tissue levels.

Adverse Effects

Adverse experiences were assessed in controlled clinical trials in which over 3600 patients received single or multiple doses of rizatriptan benzoate (as the tablet and wafer formulation). More than 1500 patients were treated in long-term extension studies for up to one year.

In clinical trials, rizatriptan benzoate was generally well-tolerated. Adverse experiences were typically mild in intensity and transient. The most common medicine-related adverse experiences were dizziness, somnolence, and asthenia/fatigue.

Table 1 lists medicine-related adverse experiences in acute Phase III trials in outpatients with migraine.

Table 1. Incidence (≥1% and Greater Than Placebo) of Medicine-Related Clinical Adverse Experiences After a Single Dose of Rizatriptan Benzoate or Placebo % of Patients			
Adverse Experiences	% of Patients		
	Rizatriptan Benzoate 5 mg (N = 977)	Rizatriptan Benzoate 10mg (N = 1167)	Placebo (N = 627)
<i>Body as a Whole</i>			
Asthenia/fatigue	3	5	1
Chest pain	2	3	1
<i>Digestive System</i>			
Dry Mouth	3	2	1
Nausea	3	4	3
Vomiting	1	1	<1
<i>Musculoskeletal System</i>			
Regional Heaviness	<1	1	<1
<i>Nervous System</i>			
Dizziness	4	8	3
Headache	1	1	<1
Paresthesia	2	3	1
Somnolence	4	8	3
<i>Respiratory System</i>			
Pharyngeal discomfort	1	2	<1
<i>Skin and Skin Appendage</i>			
Flushing	<1	1	<1

§Judged by investigator to be possibly, probably or definitely related to treatment

Additional medicine-related adverse experiences in patients taking 1 or more doses of rizatriptan benzoate 5 mg or 10 mg during acute (incidence $\geq 1\%$ and greater than placebo) or long-term (incidence $\geq 1\%$) clinical trials were, by body system:

Body as a Whole: abdominal pain

Cardiovascular: palpitation, tachycardia

Digestive: diarrhoea, dyspepsia, thirst

Musculoskeletal: neck pain, stiffness, regional tightness, muscle weakness

Nervous System: decreased mental acuity, insomnia, hypaesthesia, tremor, ataxia, nervousness, vertigo, disorientation

Respiratory: dyspnoea

Skin: pruritus, sweating

Special Senses: blurred vision

Urogenital: hot flashes.

Syncope and hypertension each occurred in $\leq 0.1\%$ of patients.

The incidences of adverse experiences were not affected by age, gender, or race (Caucasian vs. non-Caucasian). The frequencies of adverse experiences in clinical trials did not increase over time or with concomitant use of medicines commonly taken for migraine prophylaxis (including propranolol), oral contraceptives, or analgesics.

Post-Marketing Experience

The following additional adverse reactions have been reported very rarely and most have been reported in patients with risk factors predictive of CAD: myocardial ischaemia or infarction, cerebrovascular accident. The following adverse reactions have also been reported:

Hypersensitivity: hypersensitivity reaction, anaphylaxis/anaphylactoid reaction, angioedema, (e.g., facial oedema, tongue swelling, pharyngeal oedema), wheezing, urticaria, rash, toxic epidermal necrolysis

Musculoskeletal: facial pain

Special Senses: dysgeusia

Nervous System: serotonin syndrome, seizure

Vascular disorders: peripheral vascular ischaemia.

Laboratory Test Findings

In long-term controlled clinical trials, there were no clinically relevant, medicine-related changes in laboratory parameters.

Interactions

Monoamine Oxidase Inhibitors (MAOIs)

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 non-selective, irreversible MAO inhibitors. Administration of RIZAMELT to patients taking MAOIs is contraindicated (see **Contraindications**).

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 RIZAMELT should be used. Patients receiving propranolol should not take RIZAMELT 10 mg (see **Dosage and Administration**). 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

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 **Warnings and Precautions**).

Ergotamine-Type Medications

Administration of ergotamine-type medications (e.g., ergotamine, dihydro-ergotamine or methysergide) and RIZAMELT within 6 hours of each other is not recommended. 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.

Overdosage

No overdoses of rizatriptan were reported during clinical trials.

Rizatriptan 40 mg (administered as either a single dose or as two doses with a 2-hour interdose interval) was generally well tolerated in over 300 patients; dizziness and somnolence were the most common medicine-related adverse effects.

In a clinical pharmacology study in which 12 subjects received rizatriptan, at total cumulative doses of 80 mg (given within four hours), two subjects experienced syncope and/or bradycardia. One subject, a female aged 29 years, developed vomiting, bradycardia, and dizziness beginning three hours after receiving a total of 80 mg rizatriptan (administered over two hours). A third degree AV block, responsive to atropine, was observed an hour after the onset of the other symptoms. The second subject, a 25 year old male, experienced transient dizziness, syncope, incontinence, and a 5-second systolic pause (on ECG monitor) immediately after a painful venipuncture. The venipuncture occurred two hours after the subject had received a total of 80 mg rizatriptan (administered over four hours).

In addition, based on the pharmacology of rizatriptan, hypertension, angina or other more serious cardiovascular symptoms could occur after overdosage.

Treatment

Gastrointestinal decontamination (e.g., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with RIZAMELT. 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.

Actions

Rizatriptan is a potent, 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-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. Vasodilatation of these arteries and stimulation of trigeminal sensory nervous pain pathways have been postulated to be the most important underlying mechanisms in migraine pathogenesis. 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. These actions may also contribute to the clinical efficacy of rizatriptan in the relief of migraine.

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.

Pharmacokinetics

Absorption

Rizatriptan is rapidly and completely absorbed following oral administration. The mean oral bioavailability is approximately 40-45%, and mean peak plasma concentrations (C_{max}) are reached in approximately 1.6-2.5 hours (T_{max}). In clinical trials rizatriptan was administered without regard to food.

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 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 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 **Interactions**).

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 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 the 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 $t_{1/2}$, but no plasma accumulation of the medicine occurred from day to day.

Pharmaceutical Precautions

RIZAMELT orodispersible tablets

Store below 25°C.

Medicine Classification

Prescription Medicine

Package Quantities

RIZAMELT 5mg and 10 mg orodispersible tablets are available in packs of 30 tablets, in 5 blister strips with 6 orodispersible tablets each or a bottle pack.

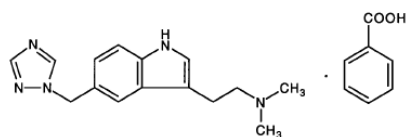
Not all pack types or strengths may be marketed.

DO NOT EAT the dessicant or the cotton wool ball contained in the packs.

Further Information

Chemistry

Rizatriptan benzoate is described chemically as: *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate. Its empirical formula is $C_{15}H_{19}N_5 \cdot C_7H_6O_2$ and its structural formula is:



Rizatriptan benzoate is a white to off-white, crystalline solid. The molecular weight of the benzoate salt is 391.47; the molecular weight of the free base is 269.4. Rizatriptan benzoate is soluble in water at about 42 mg per mL (expressed as free base) at 25°C.

Composition

RIZAMELT 5 mg and 10 mg orodispersible tablets are lactose and gluten free.

Active Ingredient

Each orodispersible tablets contains 5 mg rizatriptan (corresponding to 7.265 mg of rizatriptan benzoate), or 10 mg of rizatriptan (corresponding to 14.53 mg of rizatriptan benzoate).

Inactive Ingredients

Each orodispersible tablets contains the following inactive ingredients: colloidal anhydrous silica, crospovidone, mannitol, microcrystalline cellulose, magnesium stearate aspartame and peppermint flavour.

Name and Address

Mylan New Zealand Ltd
2B George Bourke Drive
Mt Wellington
Auckland

Tel 09 579 2792

Date of Preparation

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