

NEW ZEALAND DATA SHEET

RIZAMELT



1. Product Name

Rizamelt, 5 mg and 10 mg, orodispersible tablet

2. Qualitative and Quantitative Composition

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).

Excipient with known effect: aspartame.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

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.

4. Clinical Particulars

4.1 *Therapeutic indications*

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

4.2 *Dose and method of administration*

Dose

Clinical experience has shown that the 10 mg rizatriptan 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.

Do not halve the orodispersible tablets.

Re-dosing

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.

Special populations

Patients receiving propranolol

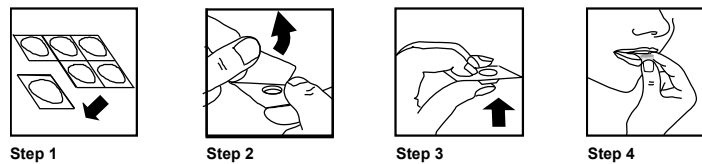
Plasma concentrations of rizatriptan may be increased by concomitant administration of propranolol (see section 4.5). The 10 mg dose is not appropriate for these patients. The physician should consider alternative therapies for these patients, for example, other 5-HT_{1B/1D} agonists that do not have this drug interaction.

Method of administration

In clinical trials rizatriptan was administered without regard to food.

The orodispersible tablets are packaged in blister strips. Patients should be instructed not to remove the tablet from the blister strip 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.



4.3 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 section 4.5).

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
- history of stroke or transient ischaemic attack (TIA)
- peripheral vascular disease, including (but not limited to) ischaemic bowel disease.

4.4 Special warnings and precautions for use

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 section 4.8). 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 section 4.3).

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 section 4.5).

Medication overuse headache

Overuse of acute migraine medications 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 migraine attacks. Detoxification of patients, including withdrawal of the overused medications, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

Reversible cerebral vasoconstriction syndrome (thunderclap headache)

Reversible cerebral vasoconstriction syndrome (thunderclap headache) has been rarely associated with serotonergic agents such as SSRIs or triptans.

Use by gender or in individuals of various ethnic origins

There is no evidence that gender or ethnic origin has any influence on the efficacy or adverse effects of rizatriptan. In controlled trials, there were no apparent differences in overall adverse experience rates or efficacy of treatment between males and females, or between various ethnic groups.

Phenylketonurics

Phenylketonuric patients should be informed that RIZAMELT orodispersible tablets contain phenylalanine (a component of aspartame). Each 5 mg RIZAMELT orodispersible tablet contains 5 mg of aspartame (2.8 mg phenylalanine), and each 10mg RIZAMELT orodispersible tablet contains 10 mg of aspartame (5.6 mg phenylalanine).

Paediatric use

Children (under 12 years of age)

There are no data available on the use of rizatriptan in children under 12 years of age. Therefore, its use in this age group is not recommended.

Adolescents (12-17 years of age)

In placebo-controlled study, the efficacy of rizatriptan tablets (5 mg) was not established. Adverse events observed in this clinical trial were similar in nature to those reported in clinical trials in adults. The use of RIZAMELT in patients under 18 years of age is not recommended.

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 ($n = 17$).

Effect on laboratory tests

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

4.5 Interaction with other medicines and other forms of interaction

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.

Cytochrome P450 isoforms

Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 isoforms 3A4/5, 2C9, 2C19, or 2E1; however, rizatriptan is a competitive inhibitor ($K_i = 1400$ nM) of cytochrome P450 2D6, (C_{max} after a 10 mg dose was 74 nM). The activity of CYP1A2 was slightly inhibited by very high (10 μ M) concentrations of rizatriptan.

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 section 4.3).

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, alternative therapy should be considered (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

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).

Paroxetine

In a study of concurrent administration of the selective serotonin reuptake inhibitor (SSRI) paroxetine 20 mg/day for two weeks, with a single dose of rizatriptan 10 mg, neither the plasma concentrations of rizatriptan nor its safety profile were affected by paroxetine.

Oral contraceptives

In a study of concurrent administration of an oral contraceptive during 6 days of administration of rizatriptan (10-30 mg/day), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone. In clinical trials, the efficacy and incidences of adverse experiences were comparable in patients taking and those not taking oral contraceptives.

Experience in migraine patients

In clinical trials, concomitant administration of medications commonly used for migraine prophylaxis did not alter the efficacy or incidences of adverse effects of rizatriptan. The overall adverse experience rates were comparable for patients on rizatriptan 5 or 10 mg who were receiving the following concomitant drugs: calcium channel blockers (n=72); tricyclic antidepressants (n=112); SSRIs (n=90); propranolol (n=108); other beta-blockers (n=175); valproic acid (n=20); opiate analgesics (n=572); oral contraceptives/estrogen replacement (n=304) as compared to those who did not receive such medications.

St John's Wort (*Hypericum perforatum*)

St John's Wort may have pharmacodynamic interactions with medicines which effect serotonin, including 5-HT_{1B/1D} agonists such as rizatriptan, used to treat migraines. These interactions may result in a variety of symptoms such as mental state change, autonomic dysfunction, and motor effects consistent with increased CNS serotonin. Therefore, RIZAMELT should be used with caution when taking St. John's Wort.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B1

Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

There are no adequate and well controlled studies of rizatriptan in pregnant women.

Rat pup birth weight was reduced when maternal animals were treated orally throughout gestation with rizatriptan at approximately 10 times the MRDD based on AUC.

In developmental studies, no teratogenic effects were observed when pregnant rats and rabbits were administered doses achieving maternal exposure approximately 215 and 115 times human exposure at the maximum recommended daily dose (MRDD), respectively, during organogenesis. Foetal weights were decreased in conjunction with decreased maternal weight gain at the highest doses. The developmental no-effect dose in these studies was at maternal exposures approximately 15 times human exposure at the MRDD in both rats and rabbits. Kinetic studies demonstrated placental transfer in both species.

RIZAMELT should be used during pregnancy only if clearly needed.

Breast-feeding

Two hours after oral administration of rizatriptan to lactating rats, the rizatriptan concentration in milk was 6 times higher than in maternal plasma. When rizatriptan was administered to lactating rats at 10 mg/kg PO (approx. 10 times anticipated maximum clinical exposure based on AUC), there was a significant reduction in pup body weight gain during lactation.

It is not known whether rizatriptan is excreted in human milk. However, caution should be exercised when RIZAMELT is administered to women who are breast-feeding.

Fertility

For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable 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 ($\geq 1\%$ and Greater Than Placebo) of Medicine-Related[§] Clinical Adverse Experiences After a Single Dose of Rizatriptan Benzoate or Placebo			
Adverse Experiences	% of Patients		
	Rizatriptan Benzoate 5 mg (N = 977)	Rizatriptan Benzoate 10 mg (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
Paresthaesia	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, myalgia

Special Senses: dysgeusia

Nervous System: serotonin syndrome, seizure

Vascular disorders: peripheral vascular ischaemia

Cardiovascular disorders: arrhythmia, bradycardia

Gastrointestinal disorders: ischaemic colitis

Investigations: ECG abnormalities.

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 professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

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.

For further advice on management of overdose please contact the National Poisons Information Centre (**0800 POISON** or **0800 764 766**).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimigraine preparations, selective serotonin (5HT₁) agonists, ATC code: N02CC04

Mechanism of action

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, possibly 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.

Pharmacodynamic effects

In healthy young male and female subjects who received maximal doses of rizatriptan (10 mg every 2 hours for three doses), slight increases in blood pressure (approximately 2-3 mmHg) were observed. These small, transient increases in blood pressure were not clinically significant. 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.

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 ischaemia 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 drug, clonidine. No effects of rizatriptan on sympathetic reflexes were demonstrated.

5.2 Pharmacokinetic properties

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}).

Administration of a 40 mg dose with a high-fat breakfast increased the extent of absorption of rizatriptan (approx.19%), but delayed the absorption by approx. 1 hour. In clinical trials rizatriptan was administered without regard to food with no apparent effect on efficacy.

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_{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.

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 \leq 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.

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: 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 m²), 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

Effects on fertility

In a fertility study in rats, altered oestrus cyclicity and delays in time to mating were observed in females treated orally with 100 mg/kg/day rizatriptan. Plasma drug exposure (AUC) at this dose was approximately 215 times the exposure in humans receiving the maximum recommended daily dose (MRDD) of 30 mg. The no-effect dose was 10 mg/kg/day (approximately 15 times the human exposure at the MRDD). There were no other fertility related effects in the female rats. There was no impairment of fertility or reproductive performance in male rats treated with up to 250 mg/kg/day (approximately 530 times the human exposure at the MRDD).

Genotoxicity

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.

Carcinogenicity

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. Exposure data were not obtained in those studies, but plasma AUC's of the parent drug were measured in other studies and indicate that exposures to the parent drug at the highest dose level would have been approximately 150 times (mice) and 240 times (rats) average AUC's measured in humans after three 10 mg doses, the maximum recommended daily dose. There was no evidence of an increase in tumour incidence related to rizatriptan in either species.

6. Pharmaceutical Particulars

6.1 *List of excipients*

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

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

6.2 *Incompatibilities*

Not applicable.

6.3 *Shelf life*

2 years

6.4 *Special precautions for storage*

Store below 25°C.

6.5 *Nature and contents of container*

RIZAMELT 5 mg 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. RIZAMELT 10 mg orodispersible tablets are also available in blister packs of 12 tablets.

Not all pack types, pack sizes or strengths may be marketed.

DO NOT EAT the desiccant or the cotton wool ball contained in the bottle pack.

6.6 *Special precautions for disposal*

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

21 October 2010

10. Date of Revision of the Text

14 December 2017

Section Changed	Summary of new information
All	Revise to SmPC format
4.2	Revised section on patients receiving Propranolol to align with Australian PI for Maxalt dated 17 February 2017.
4.3	Removed reference to 5.2
4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3	Revised to align with Australian PI for Maxalt dated 17 February 2017
6.1	Added guar gum to excipient list