

# NEW ZEALAND DATA SHEET

## my-gone

Orally disintegrating tablets, Rizatriptan benzoate, 5 mg and 10 mg (as rizatriptan)

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### Presentation

#### my-gone 5 mg

White round biconvex orally disintegrating tablets. Nominal dimensions: diameter 7.1 mm; thickness 2.4 mm. Each tablet contains rizatriptan benzoate 7.265 mg equivalent to rizatriptan 5 mg.

#### my-gone 10 mg

White round biconvex orally disintegrating tablets with score line in one side. Nominal dimensions: diameter 10.0 mm; thickness 2.9 mm. Each tablet contains rizatriptan benzoate 14.53 mg equivalent to rizatriptan 10 mg. These tablets are not intended to be divided.

### Uses

#### Pharmacotherapeutic group

N02CC04: member of N02CC - selective serotonin (5HT<sub>1</sub>) agonists, a subset of N02C – antimigraine preparations.

#### Actions

Rizatriptan is a potent, orally active serotonergic agonist that binds selectively, with high affinity, to human 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors. Rizatriptan demonstrates no clinically significant activity at 5-HT<sub>2</sub> or 5HT<sub>3</sub> receptor subtypes, nor at alpha- or beta-adrenergic, dopaminergic, histaminergic; muscarinic; or benzodiazepine receptors.

Vasodilatation of the extracerebral intracranial arteries innervated by the stimulation of trigeminal sensory nervous pain pathways have been postulated to be the most important underlying mechanisms in migraine pathogenesis. The therapeutic activity of rizatriptan in treating migraine headache is attributed to mediation of these mechanisms through cellular responses elicited by activating the 5HT<sub>1B</sub> and 5HT<sub>1D</sub> receptor subtypes.

Firstly, the agonistic effects of rizatriptan on craniovascular 5-HT<sub>1B</sub> receptors selectively constricts extracerebral intracranial arteries that may be dilated during a migraine attack. In anaesthetised dogs, rizatriptan selectively reduces carotid artery blood flow with a much lesser effect on blood flow in the coronary and pulmonary artery vasculature.

Secondly, rizatriptan also inhibits cranial sensory pathways, by activating the peripheral and central inhibitory 5-HT<sub>1D</sub> receptors that are present in animals and humans on trigeminal nerves. When stimulated, these trigeminal fibres release neuropeptides such as 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<sub>1D</sub> 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.

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Rizatriptan exerts 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<sub>2A</sub> receptors, which are known to mediate contraction in these blood vessels.

My-gone is presented as an orally disintegrating tablet enabling migraine patients to treat their migraine attacks without having to swallow liquids. This may allow patients to administer their medication earlier, for example, when liquids are not available, and to avoid possible worsening of GI symptoms by swallowing liquids.

### Pharmacokinetics

#### Absorption

Rizatriptan is rapidly and completely absorbed following oral administration. The mean oral bioavailability is approximately 40 to 45%, and the mean peak plasma levels (C<sub>max</sub>) are attained in approximately 1.6 to 2.5 hours (T<sub>max</sub>). The effect of food on the absorption of rizatriptan from orally disintegrating tablet forms has not been studied.

#### 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-monodesmethylrizatriptan, a metabolite with 5HT<sub>1B/1D</sub> receptor activity similar to that of the parent compound, is present in plasma at concentrations of approximately 14% of the parent compound but does not contribute significantly to the pharmacodynamic activity of rizatriptan 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 <sup>14</sup>C-labelled rizatriptan, rizatriptan accounts for about 17% of circulating plasma radioactivity.

#### Elimination

The plasma half-life of rizatriptan in males and females averages 2 to 3 hours. The pharmacokinetics of rizatriptan are linear in males and nearly linear in females following intravenous doses up to 60 mcg/kg. The plasma clearance of rizatriptan averages about 1000 to 1500 ml/min in males and about 900 to 1100 ml/min in females; with about 20 to 30% of this is attributed to renal clearance. Studies with <sup>14</sup>C-labelled rizatriptan indicate that about 80% of the radioactivity was recovered by renal excretion and about 10% was recovered by biliary excretion. This shows that the metabolites are excreted primarily via the kidneys.

Within the oral dose range 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

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excreted in urine as unchanged rizatriptan while 51% is excreted as the indole acetic acid metabolite. No more than 1% is excreted in urine as the active N-monodesmethyl metabolite.

If rizatriptan is administered according to the maximum dosage regimen, no drug accumulation in the plasma occurs from day to day.

### Special patient groups

#### Use in the elderly

The pharmacokinetics of rizatriptan in elderly aged up to 65 years were similar to those observed in younger adults.

### Indications

Acute treatment of migraine attacks with or without aura.

## Dosage and administration

### Dosage

Clinical experience has shown that rizatriptan 10 mg provides the optimal clinical benefit. Onset of relief, being the 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 should be used, up to a maximum of 3 doses in any 24 hour period, (refer to Interactions and Pharmacokinetics). Patients receiving propranolol should not take rizatriptan 10 mg.

### Administration

My-gone can be used in situations in which liquids are not available, or to avoid the nausea and vomiting that may accompany the ingestion of tablets with fluids. The tablets are packaged in a dual foil blister strip. Patients should be instructed to only remove a tablet from the blister strip when it is actually required and to handle the exposed tablets with dry hands. When required, the tablet should be pressed out of the blister strip in the usual manner and

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placed on the tongue, where it will melt and the solution will be swallowed with the saliva. Administration with fluids is not necessary.

### Contraindications

- Hypersensitivity to rizatriptan or to any of the ingredients in this medicine.
- Concurrent administration of monoamine oxidase (MAO) inhibitors or use within two weeks of discontinuation of MAO inhibitor therapy.
- Cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- Uncontrolled hypertension.
- Established coronary artery disease (CAD), 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.
- Peripheral vascular disease.
- Concomitant use of rizatriptan and ergotamine, ergot derivatives (including methysergide), or other 5-HT<sub>1B/1D</sub> receptor agonists.

### Warnings and precautions

Rizatriptan should only be administered to patients in whom a clear diagnosis of migraine has been established. Rizatriptan should not be administered to patients with basilar or hemiplegic migraine. Prolonged use of triptan medicines such as rizatriptan is associated with rebound headache.

Rizatriptan 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.

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

Other 5-HT<sub>1B/1D</sub> agonists such as sumatriptan should not be used concomitantly with rizatriptan and such combinations are contraindicated.

Administration of rizatriptan and ergotamine or related medicines such as dihydroergotamine or methysergide, 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.

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 rizatriptan and a SSRI such as sertraline, escitalopram, and fluoxetine or a SNRI such as venlafaxine and duloxetine, is clinically warranted, careful observation of the patient is advised, particularly during treatment

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initiation and dose increases. Serotonin syndrome symptoms may include mental status changes such as agitation, hallucinations and coma, autonomic instability manifesting as tachycardia, labile blood pressure and hyperthermia, neuromuscular aberrations such as hyperreflexia, incoordination and /or gastrointestinal symptoms such as nausea, vomiting, diarrhoea (refer to [Interactions](#)).

### **Pregnancy and lactation**

Assigned Category B1 in the Australian Categorisation of risk system. Category B1 refers to 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.

The safety of rizatriptan in human pregnancy has not been established. No treatment-related malformations or harmful effects on the development of the embryo or foetus, course of gestation, parturition and post-natal development were observed in developmental and reproductive toxicology studies conducted in rats and rabbits exposed to maternal, foetal and milk levels of rizatriptan higher than attainable from the human therapeutic dose. Since animal reproductive and developmental studies are not always predictive of human response, rizatriptan should be used during pregnancy only if clearly needed.

### **Use during lactation**

Rizatriptan is excreted in the milk of lactating rats. No data exist in humans, therefore, caution should be applied when administering rizatriptan to women who are breast-feeding. Infant exposure should be minimised by avoiding breast-feeding for 24 hours after treatment.

### **Effects on ability to drive and use machinery**

This medicine is likely to have mild to moderate effects on the ability to drive or operate machinery. 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 rizatriptan.

### **Paediatric use**

Safety and effectiveness of rizatriptan in children have not been established. Therefore, rizatriptan is not recommended for patients younger than 18 years of age.

### **Use in the elderly**

Although studies suggest the pharmacokinetics of rizatriptan in elderly aged up to 65 years are similar to those observed in younger adults, migraine occurs infrequently in the elderly and clinical experience with rizatriptan is limited in these patients. Clinical trials, demonstrated no apparent differences in efficacy or in overall adverse event rates between patients under 65 years of age and those 65 and older (n = 17).

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### Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development and pharmacokinetics and metabolism.

### Adverse effects

Rizatriptan, in oral and orally disintegrating formulations, was evaluated in over 3,600 patients for up to one year in controlled clinical studies. The most common undesirable effects evaluated in clinical studies were dizziness, somnolence, and asthenia/fatigue.

### Systemic categorisation

Undesirable effects evaluated in clinical studies and/or reported from post-marketing experience are categorised and listed below with their frequency defined by the following criteria: Very common – 1 in 10 or more; Common – from 1 in 100 to 1 in 10; Uncommon - from 1 in 1,000 to 1 in 100; Rare – from 1 in 10,000 to 1 in 1,000; Very rare – below 1 in 10,000; not known - cannot be estimated from the available data.

#### Immune system disorders

Not known: hypersensitivity reaction, anaphylaxis/anaphylactoid reaction.

#### Psychiatric disorders

Uncommon: disorientation, insomnia, nervousness.

#### Nervous system disorders

Common: dizziness, somnolence, paresthesia, headache, hypaesthesia, decreased mental acuity, tremor.

Uncommon: ataxia, vertigo.

Rare: syncope, dysgeusia/bad taste, serotonin syndrome.

Not known: seizure.

#### Eye disorders

Uncommon: blurred vision.

#### Cardiac disorders

Common: palpitation, tachycardia.

Rare: Myocardial ischaemia or infarction, cerebrovascular accident. Most of these adverse reactions have been reported in patients with risk factors predictive of coronary artery disease.

#### Vascular disorders

Common: hot flushes/flashes.

Uncommon: hypertension.

Not known: peripheral vascular ischaemia.

#### Respiratory, thoracic and mediastinal disorders

Common: pharyngeal discomfort, dyspnoea.

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Rare: wheezing.

### Gastrointestinal disorders

Common: nausea, dry mouth, vomiting, diarrhoea.

Uncommon: thirst, dyspepsia.

### Skin and subcutaneous tissue disorders

Common: flushing, sweating.

Uncommon: pruritus, urticaria.

Rare: angioedema (e.g. facial oedema, tongue swelling, pharyngeal oedema), rash, toxic epidermal necrolysis (for angioedema see also section 4.4).

### Musculoskeletal and connective tissue disorders

Common: regional heaviness.

Uncommon: neck pain, regional tightness, stiffness, muscle weakness.

Rare: facial pain.

### General disorders and administration site conditions

Common: asthenia/fatigue, pain in abdomen or chest.

## Diagnostic test results

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

## INTERACTIONS

### Microsomal enzymes

Rizatriptan does not inhibit the activities of human liver cytochrome P450 isoforms 3A4/5, 1A2, 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..

### Effects on other medicines

#### 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 selective, reversible MAO-A inhibitor. Similar or greater effects are expected with non-selective, reversible (e.g. linezolid) and irreversible MAO inhibitors. Due to a risk of coronary artery vasoconstriction and hypertensive episodes, administration of rizatriptan to patients taking inhibitors of MAO is contraindicated.

#### 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 drugs, since MAO-A plays a role in the metabolism of both rizatriptan and propranolol. This interaction leads to a mean increase in AUC and  $C_{max}$  of 70 to 80%. Patients receiving propranolol should take no more than 5 mg rizatriptan in a single dose.

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No pharmacokinetic interaction was observed between rizatriptan and the beta-blockers nadolol or metoprolol. *In vitro* data suggests no pharmacokinetic interaction should be expected with timolol or atenolol.

### Potential of ergot derivatives

Due to an additive effect, the concomitant use of rizatriptan with ergotamine, or ergot derivatives including methysergide, or other 5 HT<sub>1B/1D</sub> receptor agonists such as sumatriptan, zolmitriptan and naratriptan increase the risk of coronary artery vasoconstriction and hypertensive effects. This combination is contraindicated.

### Selective Serotonin Reuptake Inhibitors (SSRIs) /Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and Serotonin Syndrome

Cases of life-threatening serotonin syndrome during the combined use of triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs), have been reported. Refer to Warnings and precautions.

## OVERDOSAGE

### Signs and symptoms

Rizatriptan 40 mg, administered as either a single dose or as two doses separated by a two hour interval, was generally well tolerated by over 300 patients; dizziness and somnolence were the most common drug-related adverse effects reported.

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 five-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 symptomology could occur after overdose.

### Treatment

Gastro-intestinal decontamination with gastric lavage followed by activated charcoal treatment should be considered for cases of rizatriptan overdose. 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.

## PHARMACEUTICAL PRECAUTIONS

### Incompatibilities

None

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### **Storage conditions**

Unopened container

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

Opened container

Not applicable.

Reconstituted contents

Not applicable.

### **MEDICINE CLASSIFICATION**

Prescription Medicine

### **PACKAGE QUANTITIES**

My-gone 10 mg - blister strips of 3 tablets.

My-gone 5 mg - blister strips of 6 tablets. Not currently marketed.

### **FURTHER INFORMATION**

#### **List of inactive ingredients**

Microcrystalline cellulose, maize starch, silicon dioxide, aspartame (E951), mint flavour, magnesium stearate.

### **NAME AND ADDRESS**

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### **DATE OF PREPARATION**

26 July 2011

Version 1. Revisions to the previous version are indicated by (\*).