AUSTRALIAN PRODUCT INFORMATION

MAXALT® (rizatriptan benzoate)

1 NAME OF THE MEDICINE

Rizatriptan benzoate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rizatriptan benzoate is a white to off-white, crystalline solid. Rizatriptan benzoate is soluble in water at about 42 mg per mL (expressed as free base) at 25°C.

Each lyophilised wafer contains either 7.265 mg or 14.53 mg of rizatriptan benzoate (corresponding to 5 mg or 10 mg of rizatriptan, respectively).

List of excipients with known effect: mannitol, aspartame

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

5 mg wafer - White to off-white round wafer with a flat or slightly irregular surface.

10 mg wafer - White to off-white round wafer with a flat or slightly irregular surface.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

MAXALT wafers are rapidly dissolving wafers. Administration with liquid is not necessary.

The wafer is packaged in a blister within an outer aluminium sachet (pouch). Patients should be instructed not to remove the blister from the outer sachet until just prior to dosing. The blister pack should then be peeled open with dry hands and the wafer placed on the tongue, where it will dissolve and be swallowed with the saliva.

The recommended dose is 10 mg. Clinical experience has shown that this 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.

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.

Patients receiving propranolol: Plasma concentrations of rizatriptan may be increased by concomitant administration of propranolol (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions*).* 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.

4.3 CONTRAINDICATIONS

MAXALT is contraindicated in patients with:

- hypersensitivity to rizatriptan or any of the ingredients
- concurrent administration of monoamine oxidase (MAO) inhibitors, or use within 2 weeks of discontinuation of MAO inhibitor therapy (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

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

- uncontrolled hypertension
- established coronary artery disease, including ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia), signs and symptoms of ischemic heart disease, or Prinzmetal's angina.
- history of stroke or transient ischemic attack (TIA).
- peripheral vascular disease, including (but not limited to) ischemic bowel disease.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

MAXALT 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 drugs including MAXALT (see Section 4.8 Adverse Effects (Undesirable Effects)). Prior to prescribing this drug, cardiovascular assessment should be considered in patients at risk for coronary artery disease (CAD) [e.g., patients with hypertension, diabetics, smokers, and those with strong family history for CAD]. Those in whom CAD is established should not be given MAXALT (see Section 4.3 Contraindications).

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

Administration of ergotamine-type medications (e.g., ergotamine, dihydro-ergotamine or methysergide) and MAXALT 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 MAXALT 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 Interactions with Other Medicines and Other Forms of Interactions).

Overuse of acute migraine drugs 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 drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

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 MAXALT. 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 MAXALT Wafers contain phenylalanine (a component of aspartame). Each 5 mg wafer contains 1.05 mg phenylalanine, and each 10 mg wafer contains 2.10 mg phenylalanine.

Use in hepatic impairment

See Section 5.2 Pharmacokinetic Properties, Characteristics in patients, Hepatic impairment.

Use in renal impairment

See Section 5.2 Pharmacokinetic Properties, Characteristics in patients, Renal impairment.

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 MAXALT 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).

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 MAXALT 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 MAXALT in patients under 18 years of age is not recommended.

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 µM) concentrations of rizatriptan.

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 nonselective, irreversible MAO inhibitors. Administration of MAXALT to patients taking inhibitors of MAO is contraindicated (see Section 4.3 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 drugs, 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 Dose and Method of 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 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 Special Warnings and Precautions for Use).

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 MAXALT 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 MAXALT (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 MAXALT. The overall adverse experience rates were comparable for patients on MAXALT 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 MAXALT, 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, MAXALT should be used with caution when taking St. John's Wort.

4.6 FERTILITY, PREGNANCY AND LACTATION

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).

Use in 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 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.

MAXALT should be used during pregnancy only if clearly needed.

Use in lactation

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 MAXALT is administered to women who are breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse experiences were assessed in controlled clinical trials in which over 3,600 patients received single or multiple doses of MAXALT as the tablet and wafer formulation. More than 1,500 patients were treated in long-term extension studies for up to one year.

In clinical trials, MAXALT was generally well-tolerated. Adverse experiences were typically mild in intensity and transient. The most common drug-related adverse experiences were dizziness, somnolence, and asthenia/fatigue. Table 1 lists drug-related adverse experiences in acute Phase III trials in outpatients with migraine.

Table 1
Incidence (≥ 1% and Greater Than Placebo) of Drug-Related* Clinical Adverse Experiences After a Single Dose of MAXALT or Placebo

	% of Patients		
	MAXALT 5 mg (N= 977)	**MAXALT 10 mg** (N= 1167)	**Placebo** (N= 627)
Body as a Whole			
Asthenia/fatigue	3	5	1
Chest pain	2	3	1
Digestive System			
Dry Mouth	3	2	1
Nausea	3	4	3
Vomiting	1	1	<1
Musculoskeletal System			
Regional Heaviness	<1	1	<1
Nervous System			
Dizziness	4	8	3
Headache	1	1	<1
Paraesthesia	2	3	1
Somnolence	4	8	3
Respiratory System			
Pharyngeal discomfort	1	2	<1
Skin and Skin Appendage			
Flushing	<1	1	<1

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

Additional drug-related adverse experiences in patients taking 1 or more doses of MAXALT 5 mg or 10 mg during acute (incidence ≥1% and greater than placebo) or long-term (incidence ≥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, hypoaesthesia, tremor, ataxia, nervousness, vertigo, disorientation

Respiratory: dyspnoea

Skin: pruritus, sweating

Special Senses: blurred vision

Urogenital: hot flashes

Syncope and hypertension each occurred in ≤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 drugs commonly taken for migraine prophylaxis (including propranolol), oral contraceptives, or analgesics.

The adverse experience profile seen with MAXALT wafers was similar to that seen with MAXALT tablets.

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

Cardiac disorders: arrhythmia, bradycardia

Gastrointestinal disorders: ischaemic colitis

Investigations: ECG abnormalities

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

No overdoses of MAXALT were reported during clinical trials.

Rizatriptan 40 mg (administered as either a single dose or as two doses with a 2-hour inter-dose interval) was generally well tolerated in over 300 patients; dizziness and somnolence were the most common drug-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 or other more serious cardiovascular symptoms could occur after overdosage. Gastrointestinal decontamination (e.g., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with MAXALT. 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

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-$HT_{1B/1D}$ 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. 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 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.

Pharmacodynamics

In healthy young male and female subjects who received maximal doses of MAXALT (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, MAXALT 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 MAXALT, 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.

Clinical trials

MAXALT tablets

The efficacy of MAXALT tablets was established in four multicenter, randomised, placebo-controlled trials. Patients enrolled in these studies were primarily female (84%) and Caucasian (88%), with a mean age of 40 years (range of 18 to 71). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction of moderate or severe headache pain to no or mild headache pain, was assessed for up to 2 hours (Study 1) or up to 4 hours after dosing (Studies 2, 3 and 4). Associated symptoms of nausea, photophobia, and phonophobia and maintenance of response up to 24 hours post-dose were evaluated. A second dose of MAXALT tablets was allowed 2 to 24 hours after dosing for treatment of recurrent headache in Studies 1 and 2. Additional analgesics and/or antiemetics were allowed 2 hours after initial treatment for rescue in all four studies.

In all studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either MAXALT 5 or 10 mg compared to those who received placebo. In a separate study, doses of 2.5 mg were not different from placebo. Doses greater than 10 mg were associated with an increased incidence of adverse effects. The results from the 4 controlled studies using the marketed formulation are summarised in Table 2.

Table 2
Response Rates 2 Hours Following Treatment of Initial Headache

Study	Placebo	MAXALT tablets 5 mg	MAXALT tablets 10 mg
1	35% (n=304)	62%* (n=458)	71%*,** (n=456)
2†	37% (n=82)	—	77%* (n=320)
3	23% (n=80)	63%* (n=352)	—
4	40% (n=159)	60%* (n=164)	67%* (n=385)

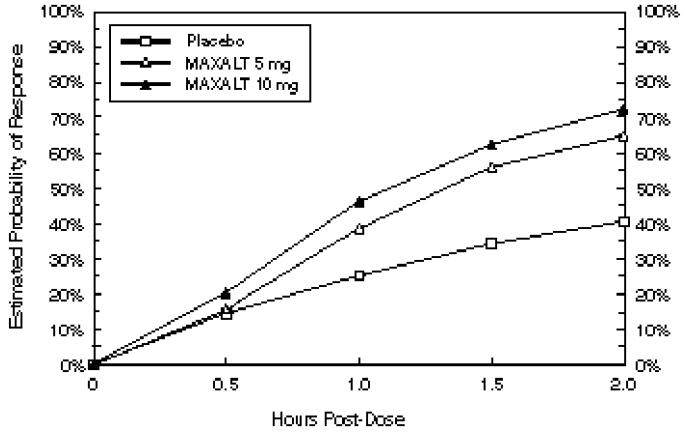
* p value < 0.05 in comparison with placebo
** p value < 0.05 in comparison with 5 mg
† Results for initial headache only

Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative

estimates of treatment response and the timing of response may be expected to vary considerably from study to study.

The estimated probability of achieving an initial headache response within 2 hours following treatment is depicted in Figure 1.

Figure 1
Estimated Probability of Achieving an Initial Headache Response by 2 Hours[††]

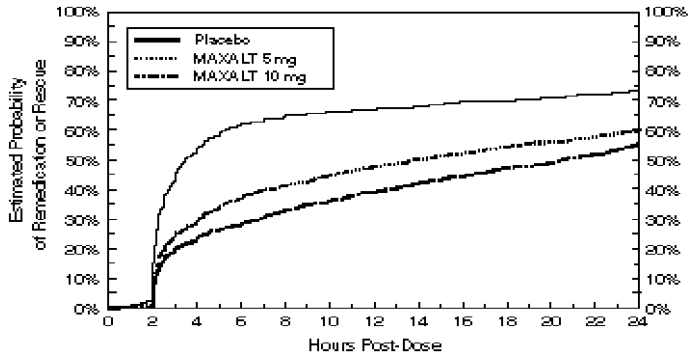


[††] Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with rizatriptan or placebo. The averages displayed are based on pooled data from 4 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 1, 2, 3, and 4). Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of MAXALT compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarised in Figure 2.

Figure 2
Estimated Probability of Patients Taking a Second Dose of MAXALT Tablets or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment[†††]



††† This Kaplan-Meier plot is based on data obtained in 4 placebo-controlled outpatient clinical trials (Studies 1, 2, 3, and 4). Patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose.
Re-medication was not allowed within 2 hours post-dose.

Efficacy was unaffected by the presence of aura; by the gender, or age of the patient; or by concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants) or oral contraceptives. There were insufficient data to assess the impact of race on efficacy.

The tablet presentation of MAXALT is no longer available.

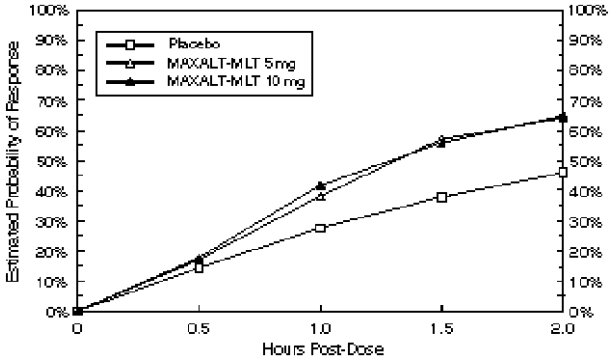
MAXALT wafers

The efficacy of MAXALT wafer 5 mg and 10 mg was demonstrated in a randomised, placebo-controlled trial that was similar in design to the trials of MAXALT tablets. Patients were instructed to treat a moderate to severe headache. Of the 312 patients treated in the study, 88% were female and 91% were Caucasian, with a mean age of 40 years (range 18-65).

By 2 hours post-dosing, response rates in patients treated with MAXALT wafer were approximately 66% in either the MAXALT 5 mg and 10 mg wafer groups, compared to 47% in the placebo group. This difference was statistically significant.

The estimated probability of achieving an initial headache response by 2 hours following treatment with MAXALT wafer is depicted in Figure 3.

Figure 3
Estimated Probability of Achieving an Initial Headache Response with MAXALT Wafer by 2 Hours‡

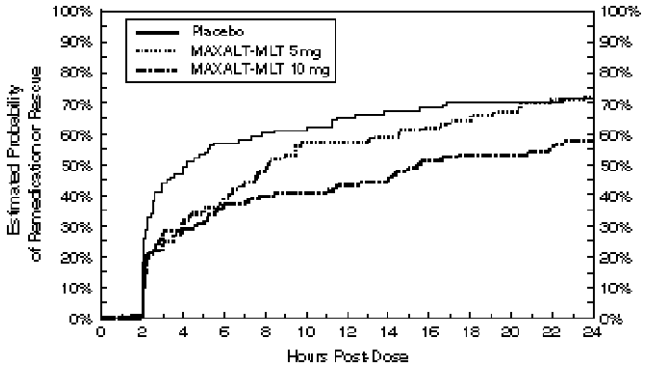


‡ Figure 3 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with MAXALT wafer or placebo. Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia and phonophobia at baseline, there was a decreased incidence of these symptoms following administration of MAXALT wafer as compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarised in Figure 4.

Figure 4
Estimated Probability of Patients Taking a Second Dose of MAXALT Wafer or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment‡‡



‡‡ In this Kaplan-Meier plot, patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Re-medication was not allowed within 2 hours post-dose.

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 MAXALT 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.

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 $5HT_{1D}$ 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.

Excretion

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 MAXALT 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 $t_{½}$, but no plasma accumulation of the drug 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 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.

5.3 PRECLINICAL SAFETY DATA

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 lyophilised wafer contains the following inactive ingredients: gelatin, mannitol, glycine, aspartame, and Peppermint NAEFCO P0551 957685 (ARTG ID: 2890).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at room temperature below 30°C. For the wafer, the patient should be instructed not to remove the blister from the outer aluminium sachet until the patient is ready to consume the wafer inside.

6.5 NATURE AND CONTENTS OF CONTAINER

5 mg wafer - Supplied in packs of 2, 3 or 6 wafers.[#]

10 mg wafer - Supplied in a starter pack of 1 wafer (sample pack only not for sale), and trade packs of 2, 3[#] or 6[#] wafers.

[#]*Presentation not currently marketed in Australia.*

MAXALT wafers are available in PVC/PVDC/Al blisters.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

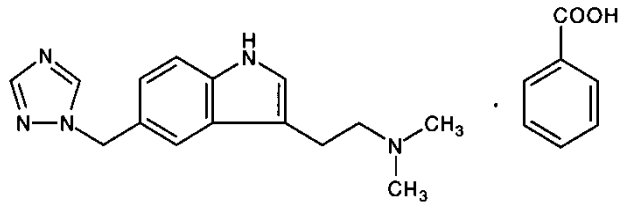
6.7 PHYSICOCHEMICAL PROPERTIES

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 $C_{15}H_{19}N_5 \bullet C_7H_6O_2$.

The molecular weight of the benzoate salt is 391.47; the molecular weight of the free base is 269.4.

Chemical structure



CAS number

CAS Number 145202-66-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (S4)

8 SPONSOR

Organon Pharma Pty Ltd
Building A, 26 Talavera Road
Macquarie Park NSW 2113

9 DATE OF FIRST APPROVAL

23 June 1999

10 DATE OF REVISION

12 January 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Amend Sponsor Details due to transfer of sponsorship