SCHEDULING STATUS

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PROPRIETARY NAME AND DOSAGE FORM

MAXALT® 5 Tablet

MAXALT® 10 Tablet

MAXALT RPD® 5 Wafer

MAXALT RPD® 10 Wafer

COMPOSITION

Each MAXALT 5 Tablet or MAXALT RPD 5 Wafer contains benzoate salt equivalent to 5 mg rizatriptan.

Each MAXALT 10 Tablet or MAXALT RPD 10 Wafer contains benzoate salt equivalent to 10 mg rizatriptan.

MAXALT Tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinised starch, ferric oxide (red) and magnesium stearate.

MAXALT Tablets contain sugar (lactose)

MAXALT RPD Wafers contain the following inactive ingredients: gelatin, mannitol, glycine, aspartame and peppermint flavour.

MAXALT RPD Wafers contain sugar alcohol (mannitol).

PHARMACOLOGICAL CLASSIFICATION

A 7.3 Vascular Medicines; Migraine Preparations.

PHARMACOLOGICAL ACTION

Pharmacodynamic Properties

Rizatriptan is a serotonergic agonist that has been shown in radioligand binding assays and functional pharmacological bioassays to act selectively at 5-HT_{1B} and 5-HT_{1D} receptors. Rizatriptan has no clinically significant activity at 5-HT_2 or 5-HT_3 receptor subtypes, nor at alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

Rizatriptan acts at craniovascular 5-HT_{1B} receptors to cause selective constriction of the extracerebral, intracranial arteries that are thought to be dilated during a migraine attack.

Rizatriptan also inhibits cranial sensory pathways, by acting at peripheral and central inhibitory 5-HT_{1D} receptors. When stimulated, these trigeminal nerves release peptides (e.g. substance P, calcitonin gene related peptide and neurokinin A), that can produce vasodilation and inflammation around blood vessels in sensitive tissues, and which relay nociceptive information into the central nervous system.

Rizatriptan has only weak partial agonist constrictor effects on human isolated coronary artery segments *in vitro*. This finding is consistent with its lack of activity at 5-HT_{2A} receptors, which are known to mediate contraction in these blood vessels.

In a study in healthy male subjects, MAXALT 10 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 ischemia was observed, as defined by standard ECG criteria. No clinically relevant ECG effects were observed.

In a study in healthy male subjects, the effects of rizatriptan, 10 and 15 mg, in a battery of tests of sympathetic reflexes were investigated in comparison to placebo and the sympatholytic medicine, clonidine. No effects of rizatriptan on sympathetic reflexes were demonstrated.

Pharmacokinetic properties

Absorption

Rizatriptan is completely absorbed following oral administration. The mean oral bioavailability of the tablet is approximately 40 - 45 %, and mean peak plasma concentrations (C_{max}) are reached in approximately 1 - 1,5 hours (T_{max}). Administration of an oral tablet dose with a high-fat breakfast had no effect on the extent of rizatriptan absorption, but absorption was slightly delayed. In clinical trials MAXALT was administered without regard to food.

The bioavailability and C_{max} of MAXALT RPD wafers are similar to that following tablet administration. The apparent rate of absorption is somewhat slower, with MAXALT RPD. In a pharmacokinetic study in adults, median T_{max} was 0,67 hours for the 10 mg tablet and 1,33 hours for the 10 mg MAXALT RPD.

Distribution

Rizatriptan is minimally bound (14 %) to plasma proteins. The volume of distribution is approximately 140 litres in male subjects, and 110 litres in female subjects.

Studies in rats indicate that rizatriptan crosses the blood-brain barrier to a limited extent.

Metabolism

The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not pharmacologically active. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the $5HT_{1B/1D}$ receptor, is formed to a minor degree, but does not contribute significantly to the pharmacodynamic activity of rizatriptan. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14 % of those of parent compound, and it is eliminated at a similar rate. Other minor metabolites include the N-oxide, the 6-hydroxy compound, and the sulfate conjugate of the 6-hydroxy metabolite. None of these minor metabolites is pharmacologically active. Following oral administration of ^{14}C- labelled rizatriptan, rizatriptan accounts for about 17 % of circulating plasma radioactivity.

Pharmacokinetic interactions: Pharmacokinetic interaction studies were carried out with the MAO-A inhibitor, moclobemide; the selective serotonin reuptake inhibitor (SSRI), paroxetine; propranolol and two other beta-blockers, nadolol and metoprolol; and oral contraceptives. Significant interactions were seen with the MAO-A inhibitor and propranolol (see **INTERACTIONS**).

Cytochrome P450 isoforms: Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 isoforms 3A4/5, IA2, 2C9, 2C19, or 2E1; however, rizatriptan is a competitive inhibitor (K_i =1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

Elimination

The plasma half-life of rizatriptan in males and females averages 2-3 hours. The pharmacokinetics of rizatriptan are linear in males and nearly linear in females following intravenous doses ≤60 mcg/kg. The plasma clearance of rizatriptan averages about 1000-1500 ml/min in males and about 900-1100 ml/min in females; about 20-30 % of this is renal clearance. Following an oral dose of ^{14}C-labelled rizatriptan, about 80 % of the radioactivity is excreted in urine, and about 10 % of the dose is excreted in faeces. This shows that the metabolites are excreted primarily via the kidneys.

After oral doses of 2,5 to 10 mg, the pharmacokinetics of rizatriptan are nearly linear. Consistent with its first-pass metabolism, approximately 14 % of an oral dose is excreted in urine as unchanged rizatriptan while 51 % is excreted as indole acetic acid metabolite.

When rizatriptan was administered every 2 hours for three doses on four consecutive days, the plasma concentrations of rizatriptan increased within each day, consistent with its $t_{½}$, but no plasma accumulation of rizatriptan occurred from day to day.

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.

INDICATIONS

MAXALT and MAXALT RPD are indicated for the acute treatment of migraine attacks with or without aura in adults.

CONTRA-INDICATIONS

MAXALT is contra-indicated in patients with:

- hypersensitivity to rizatriptan or any of the ingredients of MAXALT.
- concurrent administration of monoamine oxidase (MAO) inhibitors including linezolid, or use within 2 weeks of discontinuation of MAO inhibitor therapy (see **PHARMACOLOGICAL ACTION,** *Pharmacokinetic interactions,* **INTERACTIONS and WARNINGS AND SPECIAL PRECAUTIONS**).

Based on the mechanism of action of this class of compounds, MAXALT is also contra-indicated 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.
- MAXALT is contra-indicated in pregnancy and lactation (see **PREGNANCY AND LACTATION**).
- MAXALT is not recommended for use in paediatric patients under 18 years of age.
- history of stroke or transient ischaemic attack (TIA)
- peripheral vascular disease, including (but not limited to) ischaemic bowel disease

WARNINGS AND SPECIAL PRECAUTIONS

Rizatriptan is principally metabolised via monoamine oxidase, 'A' subtype (MAO-A). Plasma concentrations of rizatriptan and its active N-monodesmethyl metabolite were increased by

concomitant administration of a MAO~~-A~~ inhibitor including linezolid. Administration of MAXALT to patients taking inhibitors of MAO is contra-indicated (see **CONTRA-INDICATIONS and INTERACTIONS**).

In healthy young male and female subjects who received maximal doses of MAXALT (10 mg every 2 hours for three doses), [slight] transient 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.

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 reports of serious coronary events with this class of medicines including MAXALT (see **SIDE-EFFECTS**). Prior to prescribing MAXALT, 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]. Patients in whom CAD is established should not be given MAXALT (see **CONTRA-INDICATIONS**).

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 including MAXALT. If concomitant treatment with MAXALT and an SSRI (e.g., sertraline, citalopram, escitalopram, and fluoxetine) or SNRI (e.g., venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea) (see **INTERACTIONS)**.

Plasma concentrations of rizatriptan may be increased by concomitant administration of propranolol. This increase is most probably due to first-pass metabolic interaction between the two medicines, since MAO-A plays a role in the metabolism of both rizatriptan and propranolol. In adult patients receiving propranolol, the 5-mg dose of MAXALT should be used (see **DOSAGE AND DIRECTIONS FOR USE**).

Overuse of acute migraine medicines such as tryptans (including MAXALT), for 10 or more days per month, may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraines attacks. Detoxification of patients, including withdrawal of the overused medicines, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

Use in the elderly

The pharmacokinetics of rizatriptan were similar in elderly (aged ≥ 65 years) and in younger adults. In clinical trials, there were no apparent differences in efficacy or in overall adverse experience rates between patients under 65 years of age and those 65 and above (n= 17).

Effect on ability to drive or use machinery

Migraine or treatment with MAXALT may cause somnolence in some patients. Dizziness, ataxia, disorientation, blurred vision and vertigo have 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.

Lactose deficiency

MAXALT tablets contain lactose in each tablet (30,25 mg in the 5 mg tablet and 60,50 mg in the 10 mg tablet). Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency,

glucose-galactose malabsorption or fructose intolerance should not take MAXALT tablets.

Phenylketonurics

Phenylketonuric patients should be informed that MAXALT RPD 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.

INTERACTIONS

Monoamine oxidase inhibitors:

Rizatriptan is principally metabolised via monoamine oxidase, 'A' subtype (MAO-A). Plasma concentrations of rizatriptan and its active N-monodesmethyl metabolite were increased by concomitant administration of a MAO-A inhibitor including linezolid. Administration of MAXALT to patients taking inhibitors of MAO is contra-indicated (see **CONTRA-INDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS**).

Beta-Blockers:

Plasma concentrations of rizatriptan may be increased by concomitant administration of propranolol. In adult patients receiving propranolol, the 5 mg dose of MAXALT should be used (see **DOSAGE AND DIRECTIONS FOR USE**). 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 (see **WARNINGS AND SPECIAL PRECAUTIONS**)

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 tryptans (see **WARNINGS AND SPECIAL PRECAUTIONS**).

PREGNANCY AND LACTATION

MAXALT Tablets are contra-indicated in pregnant women or women who are breastfeeding their infants.

DOSAGE AND DIRECTIONS FOR USE

MAXALT Tablets

Recommended Dosing in Adults

The recommended dose in adults is 5 - 10 mg. Clinical experience has shown that a 10 mg dose provides the optimal clinical benefit, but some patients do respond to lower doses. Onset of relief (i.e., reduction of headache pain to mild or none) can occur within 30 minutes after dosing.

Redosing in adults: Doses should be separated by at least 2 hours; no more than 30 mg should be taken in any 24-hour period.

- *for headache recurrence within 24 hours:* If headache returns after relief of the initial attack, further doses may be taken. The above dosing limits should be observed.

- *after non-response:* The effectiveness of a second dose for treatment of the same attack, when an initial dose is ineffective, is not known .

Clinical studies have shown that patients who do not respond to treatment of an attack may respond to treatment for subsequent attacks.

Adult patients receiving propranolol: In patients receiving propranolol, the 5 mg dose of MAXALT should be used, up to a maximum of 3 doses in any 24-hour period (see **PHARMACOLOGICAL ACTION**, Pharmacokinetic interactions and **INTERACTIONS**).

MAXALT RPD Wafers

Recommended Dosing in Adults

MAXALT RPD may be taken as an alternative to the oral tablet, at the same recommended dosage. Administration with liquid is not necessary.

Use in Children (Under 18 years of age)

Efficacy of rizatriptan in paediatric patients under 18 years of age has not been established. Therefore, its use in this age group is not recommended.

The wafer is packaged in a blister within an outer aluminum 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.

SIDE-EFFECTS

Adults

MAXALT was evaluated in over 3600 adult patients for up to one year in controlled clinical studies. The most common side effects reported in clinical studies were dizziness,

somnolence, and asthenia/fatigue. Additional side effects reported in clinical studies include:

[Common: (≥1/100, <1/10), Uncommon: (≥1/1000, <1/100) and Rare: (≥1/10,000, <1/1,000)]

Nervous system and psychiatric disorders:

Common: Paraesthesia, headache, hypoaesthesia, decreased mental acuity, tremor.

Uncommon: Ataxia, disorientation, insomnia, nervousness, vertigo.

Rare: Syncope.

Eye disorders:

Uncommon: Blurred vision.

Cardiac disorders:

Common: Palpitation, tachycardia.

Vascular disorders:

Common: Hot flushes/flashes.

Uncommon: Hypertension.

Respiratory, thoracic and mediastinal disorders:

Common: Pharyngeal discomfort, dyspnoea.

Gastrointestinal disorders:

Common: Nausea, dry mouth, vomiting, diarrhoea.

Uncommon: Thirst, dyspepsia.

Skin and subcutaneous tissue disorders:

Common: Flushing, sweating.

Uncommon: Pruritus.

Musculoskeletal, connective tissue and bone disorders:

Common: Regional heaviness (pain, pressure, discomfort, or a strange feeling/sensation in the back, neck, jaw, upper belly or in the shoulders or arms).

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

General disorders and administration site conditions:

Common: Pain in abdomen or chest.

Post-Marketing Experience

The following additional side effects have been reported in post-marketing experience:

Immune system disorders:

Hypersensitivity reaction, anaphylaxis /anaphylactoid reaction

Nervous system and psychiatric disorders:

Dysgeusia/bad taste, serotonin syndrome, seizure

Cardiac disorders:

Myocardial ischaemia or infarction, bradycardia, dysrhythmia, cerebrovascular accident.

Most of these adverse reactions have been reported in patients with risk factors predictive of coronary artery disease.

Vascular disorders:

Peripheral vascular ischaemia

Respiratory, thoracic and mediastinal disorders:

Wheezing.

Gastro-intestinal disorders*:*

Ischaemic colitis

Skin and subcutaneous tissue disorders:

Urticaria.

Angioedema (e.g. facial oedema, tongue swelling, pharyngeal oedema), rash, toxic epidermal necrolysis.

Musculoskeletal, connective tissue and bone disorders:

Facial pain, myalgia.

***Investigations*:**

ECG abnormalities

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

No overdoses of MAXALT were reported during clinical trials in adults.

Dizziness and somnolence were the most common MAXALT related adverse effects.

Vomiting, incontinence, bradycardia and complete heart block have been reported. Hypertension and syncope have been reported. Treatment should be symptomatic and supportive

Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

The effects of haemo- or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

IDENTIFICATION

MAXALT 5 Tablet: Pale pink, capsule-shaped, convex tablet embossed with “MSD” on one side and “266” on the other side.

MAXALT 10 Tablet: Pale pink, capsule-shaped, convex tablet embossed with “MAXALT” on one side and “MSD 267” on the other side.

MAXALT RPD 5 Wafers: White to off-white round RAPIDISC with a flat or slightly irregular surface debossed with a modified (rounded) triangle on one side and a diameter of 10–11,5 mm.

MAXALT RPD 10 Wafers: White to off-white round RAPIDISC with a flat or slightly irregular surface debossed with a modified (rounded) square on one side and a diameter of 12-13,8 mm.

PRESENTATION

MAXALT Tablets are supplied in blister packs of 2, 3 and 6. The primary packaging is comprised of nylon/aluminium/polyvinyl chloride (PVC) with push through lidding of aluminium/heat seal coating (HSC). The blister packs are packed in a carton box together with package insert and patient information leaflet.

Maxalt RPD wafers are supplied in blister packs of 2, 3 and 6. The base consists of clear PVC film coated with clear PVDC. The peelable lidding material consists of paper, polyethylene terepthtalate (PET), aluminium foil and heat seal lacquer coating the aluminium foil. The sachet (paper/PE/aluminium) is formed from a film with the following composition (from the outside in): paper, laminating polyethylene, aluminium foil with low density polyethylene resin. The blisters are packed in a sachet, then a labelled carrying case which is packed into the carton box together with the package insert and patient information leaflet.

STORAGE INSTRUCTIONS

MAXALT Tablets

Store at or below 30 ˚C

Keep out of reach of children.

MAXALT RPD Wafers

Store at or below 30 °C. 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.

Keep out of reach of children.

REGISTRATION NUMBER

MAXALT 5 Tablet: 32/7.3/0534

MAXALT 10 Tablet: 32/7.3/0535

MAXALT RPD 5 Wafer: 32/7.3/0536

MAXALT RPD 10 Wafer: 32/7.3/0537

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

MSD (PTY) LTD

117 16th Street

HALFWAY HOUSE

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DATE OF PUBLICATION OF THIS PACKAGE INSERT

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