SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rizatriptan 10 mg Orodispersible Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of rizatriptan as rizatriptan benzoate.

Excipient with known effect:

Each tablet contains 10mg aspartame (E951).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible Tablet

White to off-white, round flat faced tablets with bevelled edge debossed with “M” on one side and “RN2” on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute treatment of the headache phase of migraine attacks, with or without aura in adults.

Rizatriptan Orodispersible Tablets should not be used prophylactically.

4.2 Posology and method of administration

Posology

Adults 18 years of age and older

The recommended dose is 10 mg daily.

Other medicinal products in a lower strength (5mg) are available and should be used by those patients requiring a lower dose.

Redosing: doses should be separated by at least two hours; no more than two doses should be taken in any 24-hour period.

- for headache recurrence within 24 hours: if headache returns after relief of the initial attack, one further dose 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. Therefore, if a patient does not respond to the first dose, a second dose should not be taken for the same attack.

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.

Some patients should receive the lower (5 mg) dose of Rizatriptan Orodispersible Tablets, in particular the following patient groups:

− patients on propranolol. Administration of rizatriptan should be separated by at least two hours from administration of propranolol. (see section 4.5).

− patients with mild or moderate renal insufficiency.

− patients with mild to moderate hepatic insufficiency.

Doses should be separated by at least two hours; no more than two doses should be taken in any 24-hour period.

Patients older than 65 years

The safety and efficacy of rizatriptan in patients older than 65 years have not been systematically evaluated.

Paediatric population

The safety and efficacy of rizatriptan in children and adolescents under 18 years of age has not yet been established.

Currently available data are described in sections 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration.
For oral use.

Effects of food: Onset of effect may be delayed when rizatriptan is administered in the fed state. (see section 5.2).

Rizatriptan Orodispersible Tablets need not be taken with liquid.

Rizatriptan Orodispersible Tablets are packaged in a perforated unit dose blister. Patients should be instructed to peel open the blister pack with dry hands and to place the orodispersible tablet on the tongue, where it will dissolve and be swallowed with the saliva.

Orodispersible Tablets 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 liquids.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concurrent administration of monoamine oxidase (MAO) inhibitors or use within two weeks of discontinuation of MAO inhibitor therapy (see section 4.5).

Patients with severe hepatic or severe renal insufficiency.

Patients with a previous cerebrovascular accident (CVA) or transient ischemic attack (TIA).

Moderately severe or severe hypertension, or untreated mild hypertension.

Established coronary artery disease, including ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischaemia), signs and symptoms of ischemic heart disease, or Prinzmetal's angina.

Peripheral vascular disease.

Concomitant use of rizatriptan and ergotamine, ergot derivatives (including methysergide), or other 5-$HT_{1B/1D}$ receptor agonists (see section 4.5).

4.4 Special warnings and precautions for use

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.

Rizatriptan should not be used to treat 'atypical' headaches, i.e. those that might be associated with potentially serious medical conditions, (e.g. CVA, ruptured aneurysm) in which cerebrovascular vasoconstriction could be harmful.

Rizatriptan can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat (see section 4.8). Where such symptoms are thought to indicate ischaemic heart disease, no further dose should be taken and appropriate evaluation should be carried out.

As with other 5-$HT_{1B/1D}$ receptor agonists, rizatriptan should not be given, without prior evaluation, to patients in whom unrecognised cardiac disease is likely or to patients at risk for coronary artery disease (CAD) [e.g. patients with hypertension, diabetics, smokers or users of nicotine substitution therapy, men over 40 years of age, post-menopausal women, patients with bundle branch block, and those with strong family history for CAD]. Cardiac evaluations may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease when 5-HT_1 agonists have been administered. Those in whom CAD is established should not be given rizatriptan (see section 4.3).

5-$HT_{1B/1D}$ receptor agonists have been associated with coronary vasospasm. In rare cases, myocardial ischaemia or infarction have been reported with 5-$HT_{1B/1D}$ receptor agonists including rizatriptan (see section 4.8).

Other 5-$HT_{1B/1D}$ agonists, (e.g. sumatriptan) should not be used concomitantly with rizatriptan (see section 4.5).

It is advised to wait at least six hours following use of rizatriptan before administering ergotamine-type medications (e.g. ergotamine, dihydro-ergotamine or methysergide). At least 24 hours should elapse after the administration of an ergotamine-containing preparation before rizatriptan is given. 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 (see section 4.3).

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported following concomitant treatment with triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs). These reactions can be severe. If concomitant treatment with rizatriptan and an SSRI or SNRI is clinically warranted, appropriate observation of the patient is advised, particularly during treatment initiation, with dose increases, or with addition of another serotonergic medication (see section 4.5).

Undesirable effects may be more common during concomitant use of triptans (5-$HT_{1B/1D}$ agonists) and herbal preparations containing St John's wort (Hypericum perforatum).

Angioedema (e.g. facial oedema, tongue swelling and pharyngeal oedema) may occur in patients treated with triptans, among which is rizatriptan. If angioedema of the tongue or pharynx occurs, the patient should be placed under medical supervision until symptoms have resolved. Treatment should promptly be discontinued and replaced by an agent belonging to another class of drugs.

The potential for interaction should be considered when rizatriptan is administered to patients taking CYP 2D6 substrates (see section 4.5).

<u>Medication overuse headache (MOH)</u>
Prolonged use of any painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of MOH should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

<u>Excipients</u>
This medicinal product contains aspartame, which is a source of phenylalanine. Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine. It may be harmful to patients with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

4.5 Interaction with other medicinal products and other forms of interaction

Ergotamine, ergot derivatives (including methysergide), other 5-HT $_{1B/1D}$ receptor agonists: Due to an additive effect, the concomitant use of rizatriptan and ergotamine, ergot derivatives (including methysergide), or other 5-HT $_{1B/1D}$ receptor agonists (e.g. sumatriptan, zolmitriptan, naratriptan) increase the risk of coronary artery vasoconstriction and hypertensive effects. This combination is contraindicated (see section 4.3).

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 (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 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 70-80%. In patients receiving propranolol, the 5 mg dose of Rizatriptan Orodispersible Tablets should be used (see section 4.2).

In a drug-interaction study, nadolol and metoprolol did not alter plasma concentrations of rizatriptan.

Selective Serotonin Reuptake Inhibitors (SSRIs) /Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and Serotonin Syndrome: There have been reports describing patients with symptoms compatible with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs) and triptans (see section 4.4).

In vitro studies indicate that rizatriptan inhibits cytochrome P450 2D6 (CYP 2D6). Clinical interaction data are not available. The potential for interaction should be considered when rizatriptan is administered to patients taking CYP 2D6 substrates.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative toxicity following first trimester exposure. Animal studies do not indicate reproductive toxicity (see section 5.3).

There is limited data in relation to use of rizatriptan in the second and third trimester of pregnancy. Use of rizatriptan may be considered during pregnancy, if clinically necessary.

Breast-feeding

Rizatriptan is excreted in low concentration in human milk with an average relative infant dose less than < 1 % (less than 6% in worst case scenario based on Cmax in breastmilk). Caution should be exercised when administering rizatriptan to women who are breast-feeding. Infant exposure may be minimised by avoiding breast-feeding for 12 hours after administration of Rizatriptan.

Fertility

Effects on human fertility have not been investigated. Animal studies only revealed minimal effects on fertility at plasma concentrations far in excess of human therapeutic concentrations (more than 500-fold).

4.7 Effects on ability to drive and use machines

Migraine or treatment with Rizatriptan Orodispersible Tablets 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 Orodispersible Tablets.

4.8 Undesirable effects

Summary of the safety profile

Rizatriptan was evaluated in over 8,630 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.

The following undesirable effects have been evaluated in clinical studies and/or reported in post-marketing experience:

(Very common [≥ 1/10]; Common [≥1/100 to <1/10]; Uncommon: [≥1/1,000 to <1/100]; Rare [≥1/10,000 to <1/1,000]; Very rare [<1/10,000], not known [cannot be estimated from the available data]).

System Organ Class	Frequency	Adverse Reaction
Immune system disorders	Rare	Hypersensitivity reaction, anaphylaxis/anaphylactoid reaction
Psychiatric disorders	Common	Insomnia
	Uncommon	Disorientation, insomnia, nervousness
Nervous system disorders	Common	Dizziness, somnolence, paraesthesia, headache, hypoaesthesia, decreased mental acuity

	Uncommon	Ataxia, vertigo, dysgeusia/bad taste, tremor, syncope
	Not known	Seizure, serotonin syndrome
Eye disorders	Uncommon	Blurred vision
Cardiac disorders	Common	Palpitation, tachycardia
	Uncommon	Arrhythmia, ECG abnormalities, tachycardia
	Rare	Cerebrovascular accident (most of these adverse reactions have been reported in patients with risk factors predictive of coronary artery disease), bradycardia
	Not known	Myocardial ischaemia or infarction (most of these adverse reactions have been reported in patients with risk factors predictive of coronary artery disease)
Vascular disorders	Uncommon	Hypertension, hot flushes/flashes
	Not known	Peripheral vascular ischaemia
Respiratory, thoracic and mediastinal disorders	Common	Pharyngeal discomfort, dyspnoea
	Uncommon	Dyspnoea
	Rare	Wheezing
Gastro-intestinal disorders	Common	Nausea, dry mouth, vomiting, diarrhoea, dyspepsia
	Uncommon	Thirst, dyspepsia
	Not known	Ischaemic colitis
Skin and subcutaneous tissue disorders	Common	Flushing, sweating, rash
	Uncommon	Pruritus, urticaria, urticarial, angioedema (e.g. facial oedema, tongue swelling, pharyngeal oedema) (for angioedema see also section 4.4), rash, sweating
	Not known	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Common	Regional heaviness, neck pain, stiffness
	Uncommon	Regional tightness, stiffness, muscle weakness, facial pain, myalgia
General disorders and	Common	Asthenia/fatigue, pain in abdomen

administration site conditions		or chest

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Rizatriptan 40 mg (administered as either a single dose or as two doses with a two-hour interdose interval) was generally well tolerated in over 300 adult 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 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 or other more serious cardiovascular symptoms could occur after overdose. Gastrointestinal decontamination, (e.g. gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with Rizatriptan Orodispersible Tablets. 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

Pharmacotherapeutic group: analgesics; antimigraine preparations; selective serotonin ($5\text{-}HT_1$) agonists, ATC-code: N02C C04

Mechanism of Action: Selective serotonin ($5HT_{1B/1D}$) agonists

Rizatriptan binds selectively with high affinity to human 5-HT_{1B} and 5-HT_{1D} receptors and has little or no effect or pharmacological activity at 5-HT_2, 5-HT_3; adrenergic $alpha_1$, $alpha_2$ or beta; D_1, D_2, dopaminergic, histaminic H_1; muscarinic; or benzodiazepine receptors.

The therapeutic activity of rizatriptan in treating migraine headache may be attributed to its agonist effects at 5-HT_{1B} and 5-HT_{1D} receptors on the extracerebral intracranial blood vessels that are thought to become dilated during an attack and on the trigeminal sensory nerves that innervate them. Activation of these 5-HT_{1B} and 5-HT_{1D} receptors may result in constriction of pain-producing intracranial blood vessels and inhibition of neuropeptide release that leads to decreased inflammation in sensitive tissues and reduced central trigeminal pain signal transmission.

Clinical efficacy and safety

Adults

Tablets

The efficacy of rizatriptan tablets in the acute treatment of migraine attacks was established in four multicentre, placebo-controlled trials that included over 2,000 patients who received rizatriptan 5 or 10 mg for up to one year. Headache relief occurred as early as 30 minutes following dosing, and response rates, (i.e. reduction of moderate or severe headache pain to no or mild pain) two hours after treatment were 67-77% with the 10 mg tablet, 60-63% with the 5 mg tablet, and 23-40% with placebo. Although patients who did not respond to initial treatment with rizatriptan tablets were not redosed for the same attack, they were still likely to respond to treatment for a subsequent attack. Rizatriptan reduced the functional disability and relieved the nausea, photophobia, and phonophobia associated with migraine attacks.

Rizatriptan remains effective in treating menstrual migraine, i.e. migraine that occurs within 3 days before or after the onset of menses.

Orodispersible tablets

The efficacy of a rizatriptan orodispersible tablet in the acute treatment of migraine attacks was established in two multicentre, randomised, placebo-controlled trials that were similar in design to the trials of rizatriptan tablets. In one study (n=311), by two hours post-dosing, relief rates in patients treated with rizatriptan orodispersible tablets were approximately 66% for rizatriptan 5 mg and 10 mg, compared to 47% in the placebo group. In a larger study (n=547), by two hours post-dosing, relief rates were 59% in patients treated with a rizatriptan orodispersible tablet 5 mg, and 74% after 10 mg, compared to 28% in the placebo group. A rizatriptan orodispersible tablets also relieved the disability, nausea, photophobia, and phonophobia which accompanied the migraine episodes. A significant effect on pain relief was observed as early as 30 minutes post-dosing in one of the two clinical trials for the 10 mg dose (see section 5.2).

Based on studies with the oral tablet, rizatriptan remains effective in treating menstrual migraine, i.e. migraine that occurs within 3 days before or after the onset of menses.

Paediatric population

Adolescents (12-17 years of age)
The efficacy of rizatriptan in paediatric patients (12 to 17 years of age) was evaluated in a multicenter, randomised, double-blind, placebo-controlled, parallel group study (n=570). The patient population was required to be historically non-responsive to NSAIDs and acetaminophen therapy. Patients with a qualifying migraine headache initially administered placebo or rizatriptan within 30 minutes of onset. Following the 15-minute placebo run-in, subjects who did not respond to placebo then treated a single migraine attack with placebo or rizatriptan. Using a weight-based dosing strategy, patients 20 kg to <40 kg received 5 mg rizatriptan and patients 40 kg received 10 mg rizatriptan.

In this enriched population study, a difference of 9% between active treatment and placebo was observed for the primary efficacy endpoint of pain freedom (reduction from moderate or severe pain to no pain) 2 hours after treatment (31% under rizatriptan vs. 22% for placebo (p=0.025)). No significant difference for the secondary endpoint of pain relief (reduction from moderate or severe pain to mild or no pain) was found.

Children (6-11 years of age)
The efficacy of rizatriptan was also evaluated in paediatric patients 6 to 11 years of age in the same acute placebo-controlled clinical trial (n=200). The percentage of patients achieving pain freedom 2 hours after treatment was not statistically significantly different in patients who received rizatriptan 5 and 10 mg, compared with those who received placebo (39.8% vs. 30.4%, p=0.269).

Rizatriptan Orodispersible Tablets enable 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.

5.2 Pharmacokinetic properties

Absorption

Rizatriptan is rapidly and completely absorbed following oral administration.

Tablets: 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 delayed for approximately one hour.

Orodispersible tablets: The mean oral bioavailability of the oro- dispersible tablet is approximately 40-45%, and mean peak plasma concentrations (C_{max}) are reached in approximately 1.58 hours (T_{max}).

The time to maximum plasma concentration following administration of rizatriptan as the oro- dispersible tablet formulation is delayed by 30-60 minutes relative to the tablet.

Effect of food: The effect of food on the absorption of rizatriptan from the orodispersible tablet has not been studied. For the rizatriptan tablets, Tmax is delayed by approximately 1 hour when the tablets are administered in the fed state. A further delay in the absorption of rizatriptan may occur when the orodispersible tablet is administered after meals. (see section 4.2).

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.

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 5-$HT_{1B/1D}$ receptors, 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 sulphate 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.

Elimination

Following intravenous administration, AUC in men increases proportionally and in women near-proportionally with the dose over a dose range of 10-60 µg/kg. Following oral administration, AUC increases near-proportionally with the dose over a dose range of 2.5-10 mg. The plasma half-life of rizatriptan in males and females averages 2-3 hours. The plasma clearance of rizatriptan averages about 1,000-1,500 ml/min in males and about 900-1,100 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.

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. 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.

Characteristics in patients

The following data are based on studies with the oral tablet formulation.

Patients with a migraine attack: A migraine attack does not affect the pharmacokinetics of rizatriptan.

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.

Older people: The plasma concentrations of rizatriptan observed in older subjects (age range 65 to 77 years) after tablet administration were similar to those observed in young adults.

Paediatric: A pharmacokinetics study of rizatriptan (as the oral lyophilisates formulation) was conducted in paediatric migraineurs 6 to 17 years of age. The mean exposures following a single dose administration of 5 mg rizatriptan oral lyophilisates to paediatric patients weighing 20-39 kg or 10 mg rizatriptan oral lyophilisates to paediatric patients weighing 40 kg were respectively 15% lower and 17% higher compared to the exposure observed following single dose administration of 10 mg rizatriptan oral lyophilisates to adults. The clinical relevance of these differences is unclear.

Hepatic impairment (Child-Pugh's score 5-6): Following oral tablet administration in patients with hepatic impairment caused by mild alcoholic cirrhosis of the liver, plasma concentrations of rizatriptan were similar to those seen in young male and female subjects. A significant increase in AUC (50%) and C_{max} (25%) was observed in patients with moderate hepatic impairment (Child-Pugh's score 7). Pharmacokinetics were not studied in patients with Child-Pugh's score >7 (severe hepatic impairment).

Renal impairment: In patients with renal impairment (creatinine clearance 10 - 60 ml/min/1.73 m^2), the AUC of rizatriptan after tablet administration was not significantly different from that in healthy subjects. In haemodialysis patients (creatinine clearance <10 ml/min/1.73 m^2), 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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Crospovidone (Type B)
Crospovidone (Type A)
Mannitol
Microcrystalline cellulose
Guar galactomannan

Magnesium stearate
Aspartame (E951) (see section 2 ‘Rizatriptan contains aspartame’)
Peppermint flavour (contains natural flavouring, maize maltodextrin, modified corn starch)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Rizatriptan Orodispersable Tablets are packed in OPA/Al/PVC perforated unit dose blisters of 6 x 1 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 PRODUCT LICENCE HOLDER

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8 PRODUCT LICENCE NUMBER(S)

PL 46420/0445

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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