Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rizadia 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 7.265 mg of rizatriptan benzoate (corresponding to 5 mg of the rizatriptan).

Excipient(s) with known effect
Lactose monohydrate 30.25 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Pink, capsule shaped tablets, coded MSD on one side and 266 on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Acutetreatment of the headache phase of migraine attacks with or without aura in adults.

4.2 Posology and method of administration

Method of administration

RIZADIA should not be used prophylactically.

The oral tablets should be swallowed whole with liquid.

Effect of Food: The absorption of rizatriptan is delayed by approximately 1 hour when administered together with food. Therefore, onset of effect may be delayed when rizatriptan is administered in the fed state (see also Pharmacokinetic properties, Absorption).

RIZADIA is also available as an alternative oral lyophilisate.

Posology

Adults 18 years of age and older

The recommended dose is 10 mg.

Redosing: Doses should be separated by at least 2 hours; no more than 2 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 RIZADIA, in particular the following patient groups:

- patients on propranolol. Administration of rizatriptan should be separated by at least 2 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 2 hours; no more than 2 doses should be taken in any 24-hour period.
Paediatric population
Children and Adolescents (under 18 years of age)
The safety and efficacy of RIZADIA 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.

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

4.3 Contraindications

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

Concurrent administration of monoamine oxidase (MAO) inhibitors or use within 2 weeks of discontinuation of MAO inhibitor therapy (see section 4.5).

RIZADIA is contraindicated in patients with severe hepatic or severe renal insufficiency.

RIZADIA is contraindicated in patients with a previous cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

Moderately severe or severe hypertension, or untreated mild 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.

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

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

RIZADIA 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 begiven, 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, postmenopausal 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 RIZADIA (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 RIZADIA (see section 4.8).

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

It is advised to wait at least 6 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 quantity of lactose monohydrate in each tablet is as follows: 30.25 mg in the 5-mg tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Medication overuse headache (MOH)

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.

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 contra-indicated. (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 nonselective, reversible (e.g., linezolid) and irreversible MAO inhibitors. Due to a risk of coronary artery vasoconstriction and hypertensive episodes, administration of RIZADIA 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 RIZADIA 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

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).

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 C_{max} 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 treatment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

RIZADIA (as the tablet and oral lyophilisate formulation) was evaluated in 8630 adult patients for up to one year in controlled clinical studies. The most common side effects evaluated in clinical studies were dizziness, somnolence, and asthenia/fatigue. The following side effects have been evaluated in clinical studies and/or reported in post-marketing experience:

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

Immune system disorders:
Rare: hypersensitivity reaction, anaphylaxis/anaphylactoid reaction.

Psychiatric disorders:
Common: insomnia
Uncommon: disorientation, 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.
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.
Uncommon: dyspnoea.
Rare: wheezing.

Gastrointestinal disorders:
Common: nausea, dry mouth, vomiting, diarrhoea, dyspepsia.
Uncommon: thirst.
Not known: ischaemic colitis.

Skin and subcutaneous tissue disorders:
Common: flushing.
Uncommon: pruritus, urticaria, 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, muscle weakness, facial pain, myalgia.

General disorders and administration site conditions:
Common: asthenia/fatigue,pain in abdomen 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 national reporting system listed in Appendix V.

4.9 Overdose

Rizatriptan 40 mg (administered as either a single dose or as two doses with a 2-hour interdose interval) was generally well tolerated in over 300 adult patients; dizziness and somnolence were the most common drug-related adverse effects.

In a clinical pharmacology study in which 12 adult 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 RIZADIA. 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: antimigraine preparations, selective serotonin (5HT1) 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.

Pharmacodynamic effects

Adults

The efficacy of RIZADIA Tablets in the acute treatment of migraine attacks was established in four multicenter, placebo-controlled trials that included over 2,000 patients who received RIZADIA 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) 2 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 RIZADIA were not redosed for the same attack, they were still likely to respond to treatment for a subsequent attack. RIZADIA reduced the functional disability and relieved the nausea, photophobia, and phonophobia associated with migraine attacks.

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with RIZADIA tablets in all subsets of the paediatric population in the treatment of migraine (see section 4.2 for information on paediatric use).

Adolescents (12-17 years of age)

The efficacy of RIZADIA oral lyophilisate 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 5mg 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 RIZADIA oral lyophilisate 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 RIZADIA oral lyophilisate 5 and 10 mg, compared with those who received placebo (39.8 % vs. 30.4 %, p=0.269).

5.2 Pharmacokinetic properties

Absorption
Rizatriptan is rapidly and 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 delayed for approximately one hour.

Effect of Food: The effect of food on the absorption of rizatriptan from the oral lyophilisate has not been studied. For the rizatriptan tablets, T_{max} 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 oral lyophilisate 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 sulfate conjugate of the 6-hydroxy metabolite. None of these minor metabolites is pharmacologically active. Following oral administration of ^{14}C-labeled 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-labeled 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

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.

Elderly: The plasma concentrations of rizatriptan observed in elderly subjects (age range 65 to 77 years) were similar to those observed in young adults.

Paediatric population: A pharmacokinetics study of rizatriptan (as the oral lyophilisate 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 lyophilisate to paediatric patients weighing 20-39 kg or 10 mg rizatriptan oral lyophilisate 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 lyophilisate to adults. The clinical relevance of these differences is unclear.

Hepatic impairment (Child-Pugh's score 5-6): Following oral 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 was not significantly different from that in healthy subjects. In haemodialysis patients (creatinine clearance <10 mL/min/1.73m^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

Preclinical data indicate no risk for humans based on conventional studies of repeat dose toxicity, genotoxicity, carcinogenic potential, reproductive and developmental toxicity, safety pharmacology, and pharmacokinetics and metabolism.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose (E460a)
Starch, pregelatinised
Iron oxide red (E172)
Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

All aluminium blister push through, packs of 2 tablets.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Organon Pharma (Ireland) Limited
2 Dublin Landings
North Wall Quay - North Dock
Dublin
D01 V4A3
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8 MARKETING AUTHORISATION NUMBER

PA23198/027/002

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10 DATE OF REVISION OF THE TEXT

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