RIZACT Tablets (Rizatriptan)

Composition

RIZACT Tablets 5 mg
Each film-coated tablet contains:
Rizatriptan Benzoate equivalent to Rizatriptan ............ 5 mg

RIZACT Tablets 10 mg
Each film-coated tablet contains:
Rizatriptan Benzoate equivalent to Rizatriptan ............ 10 mg

Dosage Form

Film-coated tablet

Pharmacology

Pharmacodynamics

Rizatriptan binds with high affinity to human cloned 5-HT_{1B} and 5-HT_{1D} receptors. Rizatriptan has a weak affinity for other 5-HT_{1} receptor subtypes (5-HT_{1A}, 5-HT_{1E}, 5-HT_{1F}) and the 5-HT_{3} receptor, but has no significant activity at 5-HT_{2}, 5-HT_{3}, alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

Current theories on the aetiology of migraine headache suggest that the symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from sensory nerve endings in an activated trigeminal system. The therapeutic activity of rizatriptan in migraine can most likely be attributed to agonist effects at 5-HT_{1B/1D} receptors on the extracerebral, intracranial blood vessels, which become dilated during a migraine attack, and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways.

Pharmacokinetics

Absorption

Rizatriptan is rapidly and completely absorbed following oral administration. The mean oral absolute bioavailability of the rizatriptan tablet is about 45%, and mean peak plasma concentrations (C_{max}) are reached in approximately 1–1.5 hours (T_{max}). No accumulation occurred on multiple dosing.

The area under the curve (AUC) of rizatriptan is approximately 30% higher in females than in males. The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. The T_{max} is delayed by approximately 1 hour when the tablets are administered in the fed state. In clinical trials, rizatriptan was administered without regard to food.

Distribution
The mean volume of distribution is approximately 140 litres in male subjects and 110 litres in female subjects. Rizatriptan is minimally bound (14%) to plasma proteins. No accumulation occurred on multiple dosing.

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 active at the 5-HT_{1B/1D} receptor. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-HT_{1B/1D} receptor, is formed to a minor degree. 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, the N-oxide, the 6-hydroxy compound and the sulphate conjugate of the 6-hydroxy metabolite are not active at the 5-HT_{1B/1D} receptor. None of these minor metabolites is pharmacologically active.

Following oral administration of 14C-labelled rizatriptan, rizatriptan accounts for about 17% of circulating plasma radioactivity.

Cytochrome P450 isoforms: Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 (CYP450) isoforms, 3A4/5, 1A2, 2C9, 2C19 or 2E1; rizatriptan is a competitive inhibitor (Ki=1,400 nM) of CYP450 2D6, but only at high, clinically irrelevant concentrations.

Elimination

The total radioactivity of the administered dose recovered over 120 hours in the urine and faeces was 82% and 12%, respectively, following a single 10 mg oral administration of 14C-rizatriptan. Following oral administration, the AUC increases near proportionally with the dose over a dose range of 2.5 to 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 14C-labelled rizatriptan, about 80% of the radioactivity is excreted in the urine and about 10% of the dose is excreted in the 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 the urine as unchanged rizatriptan while 51% is excreted as an indole acetic acid metabolite. No more than 1% is excreted in the urine as the active N-monodesmethyl metabolite. If rizatriptan is administered according to the maximum dosage regimen, no drug accumulation in the plasma occurs from day to day.

Special Populations

Age: Rizatriptan pharmacokinetics in healthy elderly non-migraineur volunteers (aged 65–77 years) were similar to those in younger non-migraineur volunteers (aged 18–45 years).

Gender: The AUC of rizatriptan (10 mg orally) was about 25% lower in males as compared to females, the C_{max} was 11% lower, and the T_{max} occurred at approximately the same time. This apparent pharmacokinetic difference was of no clinical significance.

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 in patients with mild hepatic impairment compared to a control group of healthy subjects. It was also similar to those seen in young male and female subjects. A significant increase in the 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). The plasma concentrations of rizatriptan were approximately 30% greater in patients with moderate hepatic impairment.

Renal Impairment: In patients with renal impairment (creatinine clearance 10–60 mL/min/1.73 m^2), the AUC_{0-∞} of rizatriptan was not significantly different from that in healthy subjects. In haemodialysis patients, (creatinine clearance <2 mL/min/1.73 m^2), however, 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.
**Race:** Pharmacokinetic data revealed no significant differences between African-American and Caucasian subjects.

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

### Indications

RIZACT Tablets are indicated for the acute treatment of migraine attacks, with or without aura, in adults and pediatric patients 6 to 17 years old.

RIZACT Tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of RIZACT Tablets have not been established for cluster headache, which is present in an older, predominantly male population.

### Dosage And Administration

In controlled clinical trials, single doses of 5 and 10 mg of rizatriptan were effective for the acute treatment of migraines in adults. There is evidence that the 10mg dose may provide a greater effect than the 5mg dose. Individuals may vary in response to doses of rizatriptan tablets. The choice of dose of RIZACT Tablets should, therefore, be made on an individual basis, weighing the possible benefit of the 10mg dose with the potential risk for increased undesirable effects.

#### Re-dosing

Doses of RIZACT Tablets should be separated by at least 2 hours; no more than 30 mg should be taken in any 24-hour period. The safety of treating, on average, more than four headaches in a 30-day period has not been established.

#### Dosing Information in Pediatric Patients (Age 6 to 17 Years)

Dosing in pediatric patients is based on the patient's body weight. RIZACT Tablets 5mg is recommended in patients weighing less than 40 kg (88 lb), and RIZACT Tablets 10mg in patients weighing 40 kg (88 lb) or more. The efficacy and safety of treatment with more than one dose of RIZACT Tablets within 24 hours in pediatric patients 6 to 17 years of age have not been established.

#### Patients Receiving Propranolol

In patients receiving propranolol, the 5mg dose of RIZACT Tablets should be used, up to a maximum of three doses in any 24-hour period.

**Pediatric Patients**

For pediatric patients (Age 6 to 17 Years) weighing 40 kg (88 lb) or more, taking propranolol, only a single dose of RIZACT Tablets 5 mg is recommended (maximum dose of 5 mg in a 24-hour period). RIZACT Tablets should not be prescribed to propranolol-treated pediatric patients who weigh less than 40 kg (88 lb).

### Contraindications

RIZACT Tablets should not be given to patients with ischaemic heart disease (e.g. angina pectoris, history of myocardial infarction or documented silent ischaemia) or to patients who have symptoms or findings consistent with ischaemic heart disease, coronary artery vasospasm, including Prinzmetal’s variant angina, or other significant underlying cardiovascular disease.

Rizatriptan increases blood pressure; therefore, RIZACT Tablets should not be given to patients with uncontrolled hypertension.

History of stroke or transient ischemic attack (TIA).

Peripheral vascular disease (PVD).
Ischemic bowel disease.
Rizatriptan increases blood pressure; therefore, RIZACT Tablets should not be given to patients with uncontrolled hypertension.
RIZACT Tablets should not be used within 24 hours of treatment with another 5-HT₁ agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.
RIZACT Tablets should not be administered to patients with haemiplegic or basilar migraine.
Concurrent administration of MAO inhibitors or use of RIZACT Tablets within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated.
RIZACT Tablets are contraindicated in patients who are hypersensitive to rizatriptan or any of its inactive ingredients.

Warnings And Precautions

General
Rizatriptan should only be used where a clear diagnosis of migraine has been established. Rizatriptan should not be administered to patients with basilar or haemiplegic migraine. As with other 5-HT₁B/₁D agonists, sensations of tightness, pain, pressure and heaviness have been reported after treatment with rizatriptan in the precordium, throat, neck and jaw. These events have not been associated with arrhythmias or definite ischaemic electrocardiogram (ECG) changes in clinical trials (one patient experienced chest pain with possible ischaemic ECG changes). Because drugs in this class may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of coronary artery disease (CAD) or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored by ECG if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischaemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT₁ agonist are candidates for further evaluation.

Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina
Rizatriptan should not be given to patients with ischemic or vasospastic coronary artery disease. There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of rizatriptan. Some of these reactions occurred in patients without known coronary artery disease (CAD). 5-HT₁ agonists, including rizatriptan may cause coronary artery vasospasm (Prinzmetal's Angina), even in patients without a history of CAD.

Triptan-naïve patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) should have a cardiovascular evaluation prior to receiving rizatriptan. If there is evidence of CAD or coronary artery vasospasm, rizatriptan should not be administered. For patients who have a negative cardiovascular evaluation, consideration should be given to administration of the first rizatriptan dose in a medically supervised setting and performing an electrocardiogram (ECG) immediately following rizatriptan administration. Periodic cardiovascular evaluation should be considered in intermittent long-term users of rizatriptan who have cardiovascular risk factors.

Arrhythmias
Life-threatening disturbances of cardiac rhythm, including ventricular tachycardia and ventricular fibrillation leading to death, have been reported within a few hours following the administration of 5-HT₁ agonists. Discontinue rizatriptan if these disturbances occur.

Chest, Throat, Neck and/or Jaw Pain/Tightness/Pressure
As with other 5-HT1 agonists, sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck and jaw commonly occur after treatment with rizatriptan and are usually noncardiac in origin. However, if a cardiac origin is suspected, patients should be evaluated. Patients shown to have CAD and those with Prinzmetal’s variant angina should not receive 5-HT1 agonists.

Cerebrovascular Events and Fatalities Associated with 5-HT1 Agonists
Cerebral haemorrhage, subarachnoid haemorrhage, stroke and other cerebrovascular events have been reported in patients treated with 5-HT1 agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g. stroke, haemorrhage, transient ischaemic attack).

Other Vasospasm-Related Events
5-HT1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischaemia and colonic ischaemia with abdominal pain and bloody diarrhoea have been reported with 5-HT1 agonists.

Increase in Blood Pressure
Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT1 agonists with and without a history of hypertension. In healthy young male and female subjects who received maximal doses of rizatriptan (10 mg every 2 hours for three doses), slight increases in blood pressure (approximately 2–3 mmHg) were observed. Rizatriptan is contraindicated in patients with uncontrolled hypertension.

Serotonin Syndrome
The development of a potentially life-threatening serotonin syndrome may occur with triptans, including rizatriptan treatment, particularly during combined use with SSRIs or SNRIs. If concomitant treatment with rizatriptan and an SSRI (e.g. fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram) or SNRI (e.g. venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases or with addition of another serotonergic medication. Serotonin syndrome symptoms may include mental status changes (e.g. agitation, hallucinations, and coma), autonomic instability (e.g. tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, and diarrhoea).

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.

Binding to Melanin-Containing Tissues
The propensity for rizatriptan to bind melanin has not been investigated. Based on its chemical properties, rizatriptan may bind to melanin and accumulate in melanin-rich tissue (e.g. eyes) over time. This raises the possibility that rizatriptan could cause toxicity in these tissues after extended use. There were, however, no adverse ophthalmologic changes related to treatment with rizatriptan in the 1-year dog toxicity study. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

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

Glucose Intolerance
Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Drug abuse and dependence
Although the abuse potential of rizatriptan has not been specifically assessed, no abuse of, toleranceto, withdrawal from, or drug-seeking behaviour was observed in patients who received rizatriptan in clinical trials or their extensions. The 5-HT<sub>1B/1D</sub> agonists, as a class, have not been associated with drug abuse.

Drug Interactions

MAO Inhibitors
Rizatriptan is principally metabolized via the MAO-A subtype. Plasma concentrations of rizatriptan and its active N-monodesmethyl metabolite may be increased by drugs that are selective MAO-A inhibitors (e.g. moclobemide) or non-selective MAO inhibitors (e.g. isocarboxazid, phenelzine, tranylcypromine and pargyline). Similar or greater effects are expected with non-selective, reversible (e.g. linezolid) and irreversible MAO inhibitors. In a drug interaction study, when rizatriptan 10 mg was administered to subjects (n=12) receiving concomitant therapy with the selective, reversible MAO-A inhibitor, moclobemide 150 mg t.i.d., there were mean increases in the rizatriptan AUC and C<sub>max</sub> of 119% and 41%, respectively; the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased more than 400%. The interaction would be expected to be greater with irreversible MAO inhibitors. No pharmacokinetic interaction is anticipated in patients receiving selective MAO-B inhibitors. Due to a risk of coronary artery vasoconstriction and hypertensive episodes, administration of rizatriptan to patients taking MAO inhibitors is contraindicated.

Ergot-containing Drugs
Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and rizatriptan within 24 hours is contraindicated. Due to an additive effect, the concomitant use of rizatriptan and ergotamine/ergot derivatives (including methysergide) increases the risk of coronary artery vasoconstriction and hypertensive effects. This combination is contraindicated.

Other 5-HT<sub>1</sub> Agonists
The administration of rizatriptan with other 5-HT<sub>1</sub> agonists (e.g. sumatriptan, zolmitriptan, naratriptan) has not been evaluated in migraine patients. Because their vasospastic effects may be additive, co-administration of rizatriptan and other 5-HT<sub>1</sub> agonists within 24 hours of each other is not recommended.

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. 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 SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans.

*In vitro* studies indicate that rizatriptan inhibits CYP450 2D6. Clinical interaction data are not available. The potential for interaction should be considered when rizatriptan is administered to patients taking CYP450 2D6 substrates.

Propranolol
Rizatriptan should be used in patients taking propranolol as propranolol has been shown to increase the plasma concentrations of rizatriptan by 70%. In a study of the concurrent administration of propranolol 240 mg/day and a single
dose of rizatriptan 10 mg in healthy subjects (n=11), the mean plasma AUC for rizatriptan was increased by 70% during propranolol administration, and a fourfold increase was observed in one subject. 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 of 70–80% in the AUC and C_max. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol.

Nadolol/Metoprolol
In a drug interaction study, the effects of multiple doses of nadolol 80 mg or metoprolol 100 mg every 12 hours on the pharmacokinetics of a single dose of 10 mg rizatriptan were evaluated in healthy subjects (n=12). No pharmacokinetic interactions were observed. In a drug interaction study, nadolol and metoprolol did not alter plasma concentrations of rizatriptan.

Paroxetine
In a study of the interaction between the SSRI, paroxetine (20 mg/day for 2 weeks) and a single dose of rizatriptan (10 mg in healthy subjects; n=12), 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 rizatriptan (10–30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl oestradiol or norethindrone.

CYP450 Isoforms
Rizatriptan is not an inhibitor of the activities of human liver CYP450 isoforms, 3A4/5, 1A2, 2C9, 2C19 or 2E1; rizatriptan is a competitive inhibitor (Ki=1,400 nM) of CYP450 2D6, but only at high, clinically irrelevant concentrations.

St. John’s Wort
Undesirable effects may be more common during concomitant use of triptans (5-HT_1B/1D agonists) and herbal preparations containing St. John’s wort.

Renal Impairment
Rizatriptan should be used with caution in dialysis patients due to a decrease in the clearance of rizatriptan.

Hepatic Impairment
Rizatriptan should be used with caution in patients with moderate hepatic impairment due to an increase in plasma concentrations of approximately 30%. For a given attack, if a patient has no response to the first dose of rizatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

Pregnancy
There are no adequate and well-controlled studies in pregnant women; therefore, rizatriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when rizatriptan are administered to women who are breastfeeding. Rizatriptan is extensively excreted in rat milk, at a level of fivefold or greater than maternal plasma levels.

Paediatric Use
Safety and effectiveness in pediatric patients under 6 years of age have not been established. The efficacy and safety of
rizatriptan in the acute treatment of migraine in patients aged 6 to 17 years was established in an adequate and well-controlled study. The incidence of adverse reactions reported for pediatric patients in the acute clinical trial was similar in patients who received rizatriptan to those who received placebo. The adverse reaction pattern in pediatric patients is expected to be similar to that in adults.

### Geriatric Use

The pharmacokinetics of rizatriptan were similar in elderly (aged 65 years or older) and in younger adults. Because migraine occurs infrequently in the elderly, clinical experience with rizatriptan is limited in such patients. In clinical trials, there were no apparent differences in efficacy or in overall adverse experience rates between patients below 65 years of age and those 65 years and above (n=17).

### Undesirable Effects

Serious cardiac events, including some that have been fatal, have occurred following use of 5-HT1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischaemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation.

The undesirable effects observed with the administration of rizatriptan are dizziness, somnolence, paraesthesia, headache, hypaesthesia, decreased mental acuity, tremor, hot flushes/flashes, pharyngeal discomfort, dyspnoea, palpitation, tachycardia, pain, tightness/pressure and/or heavy sensation in the chest, neck, throat or jaw, regional heaviness, pain in locations unspecified, dry mouth, nausea, vomiting, diarrhoea, flushing, sweating, and asthenia/fatigue.

### Incidence in Controlled Clinical Trials

Adverse experiences to rizatriptan were assessed in controlled clinical trials that included over 3700 patients who received single or multiple doses of rizatriptan Tablets. The most common undesirable effects during treatment with rizatriptan were asthenia/fatigue, somnolence, pain/pressure sensation and dizziness. These events appeared to be dose related. In long term extension studies where patients were allowed to treat multiple attacks for up to 1 year, 4% (59 out of 1525 patients) withdrew because of adverse experiences. Table 1 lists the undesirable effects regardless of drug relationship (incidence ≥ 2% and greater than placebo) after a single dose of rizatriptan. The events cited reflect experience gained under close monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behaviour, and the kinds of patients treated may differ.

Table 1-Incidence (≥ 2% and Greater than Placebo) of Adverse Experiences after a Single Dose of rizatriptan Tablets or Placebo

<table>
<thead>
<tr>
<th>Adverse Experiences</th>
<th>Rizatriptan 5mg (N=977)</th>
<th>Rizatriptan 10mg (N=1167)</th>
<th>Placebo (N=627)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical Sensations</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Parathesia</td>
<td>3</td>
<td>4</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Pain and other Pressure Sensations</td>
<td>6</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&lt;2</td>
<td>3</td>
<td>1</td>
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<td>------------------</td>
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</tr>
<tr>
<td>Chest pain:</td>
<td></td>
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<tr>
<td>Tightness/pressure and/or heaviness</td>
<td></td>
<td></td>
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<tr>
<td>Neck/throat/jaw:</td>
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<tr>
<td>Pain/tightness/heaviness</td>
<td></td>
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<td></td>
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<tr>
<td>Regional Pain:</td>
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<td></td>
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<tr>
<td>Tightness/pressure/heaviness</td>
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<td></td>
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<tr>
<td>Pain, location unspecified</td>
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<tr>
<td>Digestive</td>
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<tr>
<td>Dry Mouth</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Neurological</td>
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</tr>
<tr>
<td>Headache</td>
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<tr>
<td>Somnolence</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
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</tbody>
</table>

Rizatriptan was generally well-tolerated. Adverse experiences were typically mild in intensity and were transient. The frequencies of adverse experiences in clinical trials did not increase when up to three doses were taken within 24 hours. Adverse event frequencies were also unchanged by concomitant use of drugs commonly taken for migraine prophylaxis (including propranolol), oral contraceptives, or analgesics. The incidences of adverse experiences were not affected by age or gender. There were insufficient data to assess the impact of race on the incidence of undesirable effects.

Other Events Observed in Association with the Administration of rizatriptan

In the section that follows, the frequencies of less commonly reported adverse clinical events are presented using the following definitions: frequent undesirable effects are those defined as those occurring in at least (> ) 1/100 patients; infrequent adverse experiences are those occurring in 1/100 to 1/1000 patients; and rare adverse experiences are those occurring in fewer than 1/1000 patients.

Frequent undesirable effects: warm/cold sensations, palpitation, diarrhea, vomiting, hypesthesia, mental acuity decreased, euphoria, tremor, dyspnea, Flushing and hot flashes

Infrequent adverse experiences: chills, heat sensitivity, facial edema, hangover effect, abdominal distention, tachycardia, cold extremities, hypertension, arrhythmia, bradycardia, dyspepsia, thirst, acid regurgitation, dysphagia, constipation, flatulence, tongue edema, dehydration, muscle weakness, stiffness, myalgia, muscle cramp, musculoskeletal pain, arthralgia, muscle spasm, nervousness, vertigo, insomnia, anxiety, depression, disorientation, ataxia, dysarthria, confusion, dream abnormality, gait abnormality, irritability, memory impairment, agitation, hyperesthesia, pharyngitis, irritation (nasal), congestion(nasal), dry throat, upper respiratory infection, yawning, respiratory congestion (nasal), dry nose, epistaxis, sinus disorder, blurred vision, tinnitus, dry eyes, burning eye, eye pain, eye irritation, ear pain, tearing, sweating, pruritus, rash, urticaria, urinary frequency, polyuria and menstruation disorder.
Rare adverse experiences: Fever, orthostatic effects, syncope, edema/swelling, angina pectoris, anorexia, appetite increase, gastritis, paralysis (tongue), eructation, dysesthesia, depersonalization, akinesia/bradykinesia, apprehension, hyperkinesia, hypersomnia, hyporeflexia, cough, hicups, hoarseness, rhinorrhea, sneezing, tachypnea, pharyngeal edema, hyperacusis, smell perversion, photophobia, photopsia, itchingeye, eye swelling, erythema, acne, photosensitivity and dysuria.

Postmarketing Experience

The following section enumerates potentially important undesirable effects that have occurred in clinical practice and which have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and non-domestic use of rizatriptan. The events enumerated include all except those already listed in the UNDESIRABLE EFFECTS section above or those too general to be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of rizatriptan in their causation cannot be reliably determined.

Cardiovascular: Myocardial ischemia, myocardial infarction, peripheral vascular ischemia, ECG abnormalities.

Cerebrovascular: Stroke.

Digestive: Ischemic colitis.

Neurological/Psychiatric: Serotonin syndrome (see WARNINGS), seizure.

Special Senses: Dysgeusia.

General: Hypersensitivity reaction, anaphylaxis/anaphylactoid reaction, angioedema (e.g., faciadedema, tongue swelling, pharyngeal edema), wheezing, toxic epidermal necrolysis.

Overdosage

No overdoses of rizatriptan were reported during clinical trials. 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 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 4 hours), two of them experienced syncope and/or bradycardia. One subject, a female aged 29 years, developed vomiting, bradycardia and dizziness beginning 3 hours after receiving a total of 80 mg rizatriptan (administered over 2 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 the ECG monitor) immediately after a painful venipuncture. The venipuncture occurred 2 hours after the subject had received a total of 80 mg rizatriptan (administered over 4 hours).

In addition, based on the pharmacology of rizatriptan, hypertension or other more serious cardiovascular symptoms could occur after over dosage. Gastrointestinal decontamination, (i.e. gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with rizatriptan. Clinical and ECG monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed. The effects of haemodialysis or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

Storage And Handling Instructions

Store in a cool dry place

Packaging Information
RIZACT Tablets

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