For the use of a registered medical practitioner or a hospital or a laboratory

RIZACT

INN:
Rizatriptan benzoate

DOSAGE FORM: Tablets

COMPOSITION:
RIZACT-5
Each uncoated tablet contains
Rizatriptan benzoate equivalent to
Rizatriptan .....5 mg

RIZACT-10
Each uncoated tablet contains
Rizatriptan benzoate equivalent to
Rizatriptan .....10 mg

THERAPEUTIC CLASS:
Antimigraine

DESCRIPTION:
Light pink coloured, capsule shaped, biconvex uncoated tablets with a central breakline on one side and plain on the other side.

CLINICAL PHARMACOLOGY
Mechanism of Action
Rizatriptan binds with high affinity to human cloned 5-HT_{1B} and 5-HT_{1D} receptors. Rizatriptan has weak affinity for other 5-HT_1 receptor subtypes (5-HT_{1A}, 5-HT_{1E}, 5-HT_{1F}) and the 5-HT_7 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 etiology of migraine headache suggest that 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 that 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
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}). 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 plasma half-life of rizatriptan in males and females averages 2-3 hours.

AUC of rizatriptan is approximately 30% higher in females than in males. No accumulation occurred on multiple dosing. The mean volume of distribution is approximately 140 liters in male subjects and 110 liters in female subjects. Rizatriptan is minimally bound (14%) to plasma proteins.

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 concentration of N-monodesmethyl-rizatriptan is 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 sulfate conjugate of the 6-hydroxy metabolite are not active at the 5-HT1B/1D receptor.

The total radioactivity of the administered dose recovered over 120 hours in urine and feces was 82% and 12%, respectively, following a single 10 mg oral administration of ^{14}C-rizatriptan. Following oral administration of ^{14}C-rizatriptan, rizatriptan accounted for about 17% of circulating plasma radioactivity. Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

Cytochrome P450 Isoforms: Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 isoforms 3A4/5, 1A2, 2C9, 2C19, or 2E1; rizatriptan is a competitive inhibitor (Ki=1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

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

INDICATIONS
RIZACT is indicated for the acute treatment of migraine attacks with or without aura in adults. **RIZACT** is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine.

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

Redosing: Doses 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.

Patients receiving propranolol: In patients receiving propranolol, the 5-mg dose of **RIZACT** should be used, up to a maximum of 3 doses in any 24-hour period.

SIDE EFFECTS
The adverse experiences in clinical trials which were >2% include
Atypical Sensations: Paresthesia, *Pain and other Pressure Sensations,* Chest Pain: tightness/pressure and/or heaviness, Neck/throat/jaw: pain/ tightness/ pressure, Regional Pain: tightness/ pressure/ heaviness
Digestive: Nausea
Neurological: Dizziness, Headache, Somnolence
Other: Asthenia/fatigue
Events are further classified within body system categories

General: *Infrequent* were chills, heat sensitivity, facial edema, hangover effect, and abdominal distention. *Rare* were fever, orthostatic effects, syncope and edema/swelling.

Atypical Sensations: *Frequent* were warm/cold sensations.

Cardiovascular: *Frequent* was palpitation. *Infrequent* were tachycardia, cold extremities, hypertension, arrhythmia, and bradycardia. *Rare* was angina pectoris.

Digestive: *Frequent* were diarrhoea and vomiting. *Infrequent* were dyspepsia, thirst, acid regurgitation, dysphagia, constipation, flatulence, and tongue edema. *Rare* were anorexia, appetite increase, gastritis, paralysis (tongue), and eructation.

Metabolic: *Infrequent* dehydration.

Musculoskeletal: *Infrequent* were muscle weakness, stiffness, myalgia, muscle cramp, musculoskeletal pain, arthralgia, and muscle spasm.

Neurological/Psychiatric: *Frequent* were hypesthesia, mental acuity decreased, euphoria and tremor. *Infrequent* were nervousness, vertigo, insomnia, anxiety, depression, disorientation, ataxia, dysarthria, confusion, dream abnormality, gait abnormality, irritability, memory impairment, agitation and hyperesthesia. *Rare* were: dysesthesia, depersonalization, akinesia/bradykinesia, apprehension, hyperkinesia, hypersomnia, and hyporeflexia.

Respiratory: *Frequent* was dyspnea. *Infrequent* were pharyngitis, irritation (nasal), congestion (nasal), dry throat, upper respiratory infection, yawning, respiratory congestion (nasal), dry nose, epistaxis, and sinus disorder. *Rare* were cough, hiccups, hoarseness, rhinorrhea, sneezing, tachypnea, and pharyngeal edema.

Special Senses: *Infrequent* were blurred vision, tinnitus, dry eyes, burning eye, eye pain, eye irritation, ear pain, and tearing. *Rare* were hyperacusis, smell perversion, photophobia, photopsia, itching eye, and eye swelling.

Skin and Skin Appendage: *Frequent* was flushing. Infrequent were sweating, pruritus, rash, and urticaria. *Rare* were erythema, acne, and photosensitivity.

Urogenital system: *Frequent* was hot flushes. *Infrequent* were urinary frequency, polyuria, and menstruation disorder. *Rare* was dysuria.

WARNINGS
RIZACT should only be used where a clear diagnosis of migraine has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, **RIZACT** should not be given to patients with documented ischemic or vasospastic coronary artery disease. It is strongly recommended that rizatriptan not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors

Cardiac Events and Fatalities Associated with 5-HT$_1$ Agonists: Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low.

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Cerebrovascular Events and Fatalities Associated with 5-HT$_1$ Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with other 5-HT_1 agonists; and some have resulted in fatalities. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Other Vasospasm-Related Events: 5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT_1 agonists.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT_1 agonists with and without a history of hypertension.

PRECAUTIONS
General
Patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT_1 agonist are candidates for further evaluation.

Rizatriptan should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs.

Renally Impaired Patients: Rizatriptan should be used with caution in dialysis patients due to a decrease in the clearance of rizatriptan.

Hepatically Impaired Patients: Rizatriptan should be used with caution in patients with moderate hepatic insufficiency due to an increase in plasma concentrations of approximately 30%,

Binding to Melanin-Containing Tissues
Based on its chemical properties, rizatriptan may bind to melanin and accumulate in melanin rich tissue (e.g., eye) over time. There were, however, no adverse ophthalmologic changes related to treatment with rizatriptan in the one year dog toxicity study. The prescriber should be aware of the possibility of long-term ophthalmologic effects.

Laboratory Tests
No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with Rizatriptan.

Drug Interactions
Monoamine oxidase inhibitors: Plasma concentrations of rizatriptan may be increased by drugs that are selective MAO-A inhibitors (e.g., moclobemide) or nonselective MAO inhibitors [type A and B] (e.g., isocarboxazid, phenelzine, tranylcypromine, and pargyline).

Propranolol: In a study, mean plasma AUC for rizatriptan was increased by 70% during propranolol administration, and a fourfold increase was observed in one subject. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol.

Nadolol/Metoprolol: In a drug interactions study, 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.

Oral contraceptives: Rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

Ergot-containing drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Hence use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and rizatriptan within 24 hours is contraindicated.

Other 5-HT$_1$ agonists: The administration of rizatriptan with other 5-HT_1 agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, coadministration of rizatriptan and other 5-HT_1 agonists within 24 hours of each other is not recommended.

Selective serotonin reuptake inhibitors (SSRIs): SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT_1 agonists.

Drug/Laboratory Test Interactions
Rizatriptan is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: There was no evidence of an increase in tumor incidence related to rizatriptan in either species.

Mutagenesis: Rizatriptan, with and without metabolic activation, was neither mutagenic, nor clastogenic in a battery of in vitro and in vivo genetic toxicity studies.

Impairment of Fertility: There was no impairment of fertility or reproductive performance in male rats treated with up to 250 mg/kg/day.

Pregnancy
Pregnancy Category C
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 fetus.

Nursing Mothers
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 **RIZACT** is administered to women who are breast-feeding.

Pediatric Use
Safety and effectiveness of rizatriptan in pediatric patients have not been established; therefore, **RIZACT** is not recommended for use in patients under 18 years of age.

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

OVERDOSE
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 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, (i.e., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with rizatriptan Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

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

CONTRAINDICATIONS
RIZACT should not be given to patients with ischemic heart disease or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease.

Because **RIZACT** may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

RIZACT 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** should not be administered to patients with hemiplegic or basilar migraine.

Concurrent administration of MAO inhibitors or use of rizatriptan within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated. **RIZACT** is contraindicated in patients who are hypersensitive to rizatriptan or any of its inactive ingredients

PACKING/PACKSIZE:
RIZACT
Packing: Carton containing blister of 4 tablets
Packsize: Blister of 4 tablets

Storage condition, user instruction and pharmaceutical precaution:
STORAGE:
Store below 30°C. Protect from moisture.

EXPIRY: 2 years

PRESENTATION:
RIZACT-5 ……..... Blister of 4 tablets
RIZACT-10 ……..... Blister of 4 tablets

Cipla

Mfd. by **CIPLA LTD.**
Unit I Malpur, Dist Solan
173205 INDIA.

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PACKAGING DEVELOPMENT

Product Name : Rizact	Item Code : xxxxxxxx	Item : Encl	Date : 05-02-2016
Coordinator : Dipali	Artist : Manish	Software : Illustrator CC	
Fonts : ----------			
Colours : BLUE WOOL TEST VALUE 5-8 (LIGHT FASTENING DATA)	Black INK: Oil based Ink from DIC OR MICRO		
Spectro-Densitometer Delta-E reading (△E) for colour: NOT MORE THAN dE2.5	Glossmeter reading (for white surface): NOT LESS THAN 80 %		
Supersedes / Reference : C821F	Screen : # __	Unwinding Direction : --------	
Tuck flap: ---------	Side / Collar flap overlap: ----------	Caliper (Thickness) for Board: ----------	
Links : ----------			
Pharmacode : NA		Design : Unfolded	
Material : 54 gsm Maplitho Paper		Varnish : ----------	
Actual Size : 120 x 260 mm		Size after Folding : -------	
Print repeat length : ----------			
Grain Direction : Parallel to printing length			
Reference / Instructions / Remark / Braille Text Embossing: ----------			
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NOTE TO THE PRINTER :
- Return approved artwork alongwith the proof.
- The proof must be verified against the approved hardcopy, should be certified and signed by an authorised QA person. The unsigned proof will not be accepted.
- Colour scheme must be as approved by packaging development co-ordinator.
- Any deviation must be brought to the notice of packaging development co-ordinator immediately.
- For any clarification, please contact packaging development co-ordinator immediately