Other Vasospasm-Related Events, Including Peripheral Vascular Ischemia and Colonic Ischemia Triptans, including ALMOTRIPTAN, may cause vasospastic reactions other than coronary artery vasospasm, such as peripheral and gastrointestinal vascular ischemia with abdominal pain and bloody diarrhea. Very rare reports of transient and permanent blindness and significant partial vision loss have been reported with the use of triptans. Visual disorders may also be part of a migraine attack. Patients who experience symptoms or signs suggestive of decreased arterial flow following the use of any triptan, such as ischemic bowel syndrome or Raynaud's syndrome, are candidates for further evaluation.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome may occur with triptans, including ALMOTRIPTAN, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). If concomitant treatment with ALMOTRIPTAN 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. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea)

Increases in Blood Pressure

As with other triptans, significant elevations in systemic blood pressure have been reported on rare occasions with ALMOTRIPTAN use inpatients with and without a history of hypertension; very rarely these increases in blood pressure have been associated with significant clinical events. ALMOTRIPTAN is contraindicated in patients with uncontrolled hypertension. In normotensive healthy subjects and patients with hypertension controlled by medication, small, but clinically insignificant, increases in mean systolic (0.21 and 4.87 mm Hg, respectively) and diastolic (1.35 and 0.26 mm Hg, respectively) blood pressure relative to placebo were seen over the first 4 hours after oral administration of 12.5 mg of almotriptan.

An 18% increase in mean pulmonary artery pressure was seen following dosing with another triptan in a study evaluating subjects undergoing cardiac catheterization.

Hypersensitivity to Sulfonamides

Caution should be exercised when prescribing ALMOTRIPTAN to patients with known hypersensitivity to sulfonamides. The chemical structure of almotriptan contains a sulfonyl group, which is structurally different from a sulfonamide. Cross-sensitivity to almotriptanin patients allergic to sulfonamides has not been systematically evaluated.

Impaired Hepatic or Renal Function

ALMOTRIPTAN should be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as those with impaired hepatic or renal function

Binding to Melanin-Containing Tissues

When pigmented rats were given a single oral dose of 5 mg/kg of radio labeled almotriptan, the elimination half-life of radioactivity from the eye was 22 days. This finding suggests that almotriptan and/or its metabolites may bind to melanin in the eye. Because almotriptan could accumulate in melanin-rich tissues over time, there is the possibility that it could cause toxicity in these tissues with extended use. However, no adverse retinal effects related to treatment with almotriptan were noted in a 52-week toxicity study in dogs given up to 12.5 mg/kg/day (resulting in exposure [AUC] to parent drug approximately 20 times that in humans receiving the maximum recommended human dose of 25 mg/day). 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.

Corneal Opacities

Three male dogs (out of a total of 14 treated) in a 52-week toxicity study of oral almotriptan developed slight corneal opacities that were noted after 51 weeks, but not after 25 weeks of treatment. The doses at which this occurred were 2, 5, and 12.5 mg/kg/day. The opacity reversed after a 4-week drug-free period in the affected dog treated with the highest dose. Systemic exposure (plasma AUC) to parent drug at 2 mg/kg/day was approximately 2.5 times the exposure in humans receiving the maximum recommended human daily dose of 25 mg. A no-effect dose was not established

OVER DOSAGE

Signs and Symptoms

Patients and volunteers receiving single oral doses of 100 to 150 mg of almotriptan did not experience significant adverse events. Six additional normal volunteers received single oral doses of 200 mg without serious adverse events. During clinical trials with ALMOTRIPTAN (almotriptan malate), one patient ingested 62.5 mg in a 5-hour period and another patient ingested 100 mg in a 38-hour period. Neither patient experienced adverse reactions.

Based on the pharmacology of triptans, hypertension or other more serious cardiovascular symptoms could occur after over dosage.

Recommended Treatment

Gastrointestinal decontamination (i.e., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with ALMOTRIPTAN. Clinical and electrocardiographic monitoring should be continued for at least 20 hours even if clinical symptoms are not observed.

It is unknown what effect hemodialysis or peritoneal dialysis has on plasma concentrations of almotriptan.

STORAGE:

Store below 25°C.
Protect from light and moisture

Manufactured by:
MSN Laboratories Private Limited
(Formulations Division), Plot No. 42, Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325, Telangana, INDIA.

B3553-01

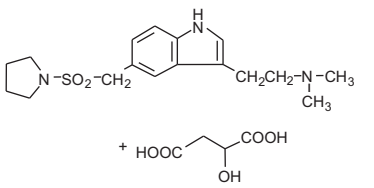
Almotriptan Tablets 6.25/12.5 mg

Label Claim
ALMOTAN - 6.25 अल्मोटान ६.२५
Each film coated tablet contains:
Almotriptan malate equivalent to
Almotriptan....6.25 mg
Colours: Iron Oxide Yellow & Titanium Dioxide IP

Label Claim
ALMOTAN - 12.5 अल्मोटान १२.५
Each film coated tablet contains:
Almotriptan malate equivalent to
Almotriptan....12.5 mg
Colour: Titanium Dioxide IP

Chemical Name: 1-[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]methyl]sulfonyl]pyrrolidine (±)-hydroxybutanedioate (1:1)

Structural formula is:



Empirical formula : C17H25N3O2S-C4H6O5
Molecular weight : 469.56.

PHARMACOLOGY

Pharmacodynamics:

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 almotriptan in migraine can most likely be attributed to agonist effects at 5-HT1B/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

Absorption:

The absolute bioavailability of almotriptan is about 70%, with peak plasma levels occurring 1 to 3 hours after administration; food does not affect pharmacokinetics. Distribution Almotriptan is minimally protein bound (approximately 35%) and the mean apparent volume of distribution is approximately 180 to 200 liters.

Metabolism

Almotriptan is metabolized by two major and one minor pathways. Monoamine oxidase (MAO)-mediated oxidative deamination (approximately 27% of the dose), and cytochrome P450-mediated oxidation (approximately 12% of the dose) are the major routes of metabolism, while flavin monooxygenase is the minor route. MAO-A is responsible for the formation of the indoleacetic acid metabolite, whereas cytochrome P450 (3A4 and 2D6) catalyzes the hydroxylation of the pyrrolidine ring to an intermediate that is further oxidized by aldehyde dehydrogenase to the gamma-aminobutyric acid derivative. Both metabolites are inactive.

Excretion

Almotriptan has a mean half-life of 3 to 4 hours. Almotriptan is eliminated primarily by renal excretion (about 75% of the oral dose), with approximately 40% of an administered dose excreted unchanged in urine. Renal clearance exceeds the glomerular filtration rate by approximately 3-fold, indicating an active mechanism. Approximately 13% of the administered dose is excreted via feces, both unchanged and metabolized.

Drug-Drug Interactions

All drug interaction studies were performed in healthy volunteers using a single 12.5 mg dose of almotriptan and multiple doses of the other drug. Monoamine Oxidase Inhibitors Co-administration of almotriptan and moclobemide (150 mg twice daily for 8 days) resulted in a 27% decrease in almotriptan clearance and an increase in Cmax of approximately 6%. No dose adjustment is necessary.

Propranolol

Co-administration of almotriptan and propranolol (80 mg twice daily for 7 days) resulted in no significant changes in the pharmacokinetics of almotriptan.

Fluoxetinepage 11 of 19 Co-administration of almotriptan and fluoxetine (60 mg daily for 8 days), a potent inhibitor of CYP2D6, had no effect on almotriptan clearance, but maximal concentrations of almotriptan were increased 18%. This difference is not clinically significant.

Verapamil

Co-administration of almotriptan and verapamil (120 mg sustained-release tablets twice daily for 7 days), an inhibitor of CYP3A4, resulted in a 20% increase in the area under the plasma concentration-time curve, and in a 24% increase in maximal plasma concentrations of almotriptan. Neither of these changes is clinically significant. No dose adjustment is necessary. Ketoconazole and other Potent CYP3A4 Inhibitors Co-administration of almotriptan and ketoconazole, a potent CYP3A4 inhibitor, resulted in an approximately 60% increase in exposure of almotriptan. Increased exposures to almotriptan may be expected when almotriptan is used with other potent CYP3A4 inhibitors. Special Populations.

Geriatric

Renal and total clearance, and amount of drug excreted in the urine, were lower in elderly healthy volunteers (age 65 to 76 years) than in younger healthy volunteers (age 19 to 34 years), resulting in longer terminal half-life (3.7 hours vs. 3.2 hours) and a 25% higher area under the plasma concentration-time curve in the elderly subjects. The differences, however, do not appear to be clinically significant.

Pediatric

A pharmacokinetics study of almotriptan was conducted in adolescents (12 to 17 years) and adults (18 to 55 years) with or without a history of migraine. No differences were observed in the rate or extent of absorption of almotriptan in adolescents compared with adults.

Gender

No significant gender differences were observed in pharmacokinetic parameters.

Race

No significant differences were observed in pharmacokinetic parameters between Caucasian and African-American volunteers. Hepatic Impairment.

The pharmacokinetics of almotriptan have not been assessed in patients with hepatic impairment. Based on the known mechanisms of clearance of almotriptan, the maximum decrease expected in almotriptan clearance due to hepatic impairment would be 60%.

Renal Impairment

The clearance of almotriptan was approximately 65% lower in patients with severe renal impairment (Cl/F=19.8 L/hour; creatinine clearance between 10 and 30 mL/min) and approximately 40% lower in patients with moderate renal impairment (Cl/F=34.2 L/hour; creatinine clearance between 31 and 71 mL/min) than in healthy volunteers (Cl/F=57 L/hour). Maximal plasma concentrations of almotriptan increased by approximately 80% in these patients.

INDICATIONS AND USAGE

Acute Treatment of Migraine Attacks Adults

ALMOTRIPTAN (almotriptan malate) is indicated for the acute treatment of migraine attacks in patients with a history of migraine with or without aura.

Adolescents Age 12 to 17 Years.

ALMOTRIPTAN is indicated for the acute treatment of migraine headache pain in patients with a history of migraine attacks with or without aura usually lasting 4 hours or more (when untreated).

Important Limitations ALMOTRIPTAN should only be used where a clear diagnosis of migraine has been established. If a patient has no response for the first migraine attack treated with ALMOTRIPTAN, the diagnosis of migraine should be reconsidered before ALMOTRIPTAN is administered to treat any subsequent attacks.

In adolescents age 12 to 17 years, efficacy of ALMOTRIPTAN on migraine-associated symptoms (nausea, photophobia, and phonophobia) was not established. ALMOTRIPTAN is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine Safety and effectiveness of ALMOTRIPTAN have not been established for cluster headache which is present in an older, predominantly male population.

DOSAGE AND ADMINISTRATION

Acute Treatment of Migraine Attacks

The recommended dose of ALMOTRIPTAN (almotriptan malate) in adults and adolescents age 12 to 17 years is 6.25 mg to 12.5 mg, with the 12.5 mg dose tending to be a more effective dose in adults. As individuals may vary in their response to different doses of ALMOTRIPTAN,the choice of dose should be made on an individual basis.If the headache is relieved after the initial ALMOTRIPTAN dose but returns, the dose may be repeated after 2 hours. The effectiveness of a second dose has not been established in placebo-controlled trials. The maximum daily dose should not exceed 25 mg. The safety of treating an average of more than four migraines in a 30-day period has not been established.

Hepatic Impairment

The recommended starting dose of ALMOTRIPTAN in patients with hepatic impairment is 6.25 mg. The maximum daily dose should not exceed 12.5 mg over a 24-hour period.

Renal Impairment

The recommended starting dose of ALMOTRIPTAN in patients with severe renal impairment is 6.25 mg. The maximum daily dose should not exceed 12.5 mg over a 24-hour period

CONTRAINDICATIONS

Ischemic or Vasospastic Coronary Artery Disease, or Other Significant Underlying Cardiovascular Disease Do not use ALMOTRIPTAN (almotriptan malate) in patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia), or in patients who have symptoms or findings consistent with ischemic heart disease, coronaryartery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease.

Cerebrovascular Syndromes Do not use ALMOTRIPTAN in patients with cerebrovascular syndromes including (but not limited to) stroke of any type as well as transient ischemic attacks.

Peripheral Vascular Disease Do not use ALMOTRIPTAN in patients with peripheral vascular disease including (but not limited to) ischemic bowel disease.

Uncontrolled Hypertension Because ALMOTRIPTAN may increase blood pressure, do not use ALMOTRIPTAN in patients with uncontrolled hypertension.

Ergotamine-Containing and Ergot-Type Medications

Do not use ALMOTRIPTAN and ergotamine-containing or ergot-derived medications like dihydroergotamine, ergotamine tartrate, or methysergide within 24 hours of each other.

Concomitant Use With 5-HT1 Agonists (e.g., Triptans)

ALMOTRIPTAN and other 5-HT1 agonists (e.g., triptans) should not be administered within 24 hours of each other.

Hemiplegic or Basilar Migraine

Do not use ALMOTRIPTAN in patients with hemiplegic or basilar migraine.

Hypersensitivity

ALMOTRIPTAN is contraindicated in patients with known hypersensitivity to almotriptan or any of its inactive ingredients.

WARNINGS AND PRECAUTIONS

Risk of Myocardial Ischemia and Infarction and Other Adverse Cardiac Events Cardiac Events and Fatalities with 5-HT1 Agonists Serious adverse cardiac events, including acute myocardial infarction, have been reported within a few hours following administration of ALMOTRIPTAN (almotriptan malate). Life-threatening disturbances of cardiac rhythm and death have been reported within a few hours following the administration of other triptans. Considering the extent of use of triptans in patients with migraine, the incidence of these events is extremely low.

ALMOTRIPTAN can cause coronary vasospasm; at least one of these events occurred in a patient with no cardiac history and with documented absence of coronary artery disease. Because of the close proximity of the events to use of ALMOTRIPTAN, a causal relationship cannot be excluded. 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 electrocardiographically if dosing is resumed and similar symptoms recur. Premarketing Experience with ALMOTRIPTAN in Adults Among the 3865 subjects/patients who received ALMOTRIPTAN in premarketing clinical trials, one patient was hospitalized for observationafter a scheduled electrocardiogram (ECG) was found to be abnormal (negative T-waves on the left leads) 48 hours after taking a single 6.25 mg dose of almotriptan. The patient, a 48-year-old female, had previously taken 3 other doses for earlier migraine attacks.

Myocardial enzymes at the time of the abnormal ECG were normal. The patient was diagnosed as having had myocardial ischemia and that she had a family history of coronary disease. An ECG performed 2 days later was normal, as was a follow-up coronary angiography. The patient recovered without incident.

Postmarketing Experience with ALMOTRIPTAN in Adults Serious cardiovascular events have been reported in association with the use of ALMOTRIPTAN. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to definitively determine the proportion of the reported cases that were actually caused by almotriptan or to reliably assess causation in individual cases.

Patients with Documented Coronary Artery Disease because of the potential of this class of compound (5-HT1 agonists) to cause coronary vasospasm, ALMOTRIPTAN should not be given to MI patients with documented ischemic or vasospastic coronary artery disease.

Patients with Risk Factors for CAD It is strongly recommended that ALMOTRIPTAN not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, ALMOTRIPTAN should not be administered.

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of ALMOTRIPTAN take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received ALMOTRIPTAN. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an ECG during the interval immediately following ALMOTRIPTAN, in these patients with risk factors. It is recommended that patients who are intermittent long-term users of ALMOTRIPTAN and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use AXERT.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to ALMOTRIPTAN. The ability of cardiac diagnostic procedures to detect all cardiovascular diseases or predisposition to coronary artery vasospasm is modest at best. Cardiovascular events associated with triptan treatment have occurred in patients with no cardiac history and with documented absence of coronary artery disease.

Sensations of Pain, Tightness, Pressure in the Chest and/or Throat, Neck, and Jaw As with other 5-HT1 agonists, sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw have been reported after treatment with ALMOTRIPTAN. Because 5-HT1 agonists may cause coronary vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms occur. Patients shown to have CAD and those with Prinzmetal's variant angina should not receive 5-HT1 agonists.

Cerebrovascular Events and Fatalities

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with other triptans and some events have resulted in fatalities. In a number of cases, it appeared possible that the cerebrovascular events were primary, the triptan having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g.,stroke, hemorrhage, and transient ischemic attack).