

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

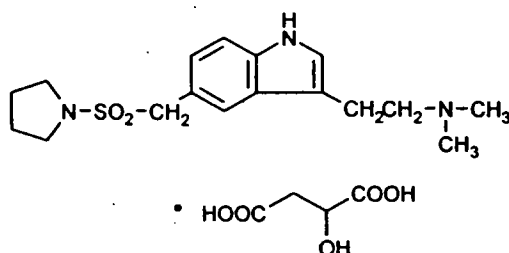
APPLICATION NUMBER:

21-001

APPROVED DRAFT LABELING

DESCRIPTION

AXERT Tablets contain almotriptan malate, a selective 5-hydroxytryptamin_{B/ID} (5-HT_{1B/1D}) receptor agonist. Almotriptan malate is chemically designated as 1-[[[3-[2-(Dimethylamino)ethyl]-1H-indol-5yl]methyl]sulfonyl]pyrrolidine (±)-hydroxybutanedioate (1:1), and its structural formula is:



Its empirical formula is C₁₇H₂₅N₃O₂S·C₄H₆O₅, representing a molecular weight of 469.56. Almotriptan is a white to slightly yellow crystalline powder that is soluble in water. AXERT Tablets for oral administration contain almotriptan malate equivalent to 6.25 or 12.5 mg of almotriptan. Each compressed tablet contains the following inactive ingredients: mannitol, cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, titanium dioxide, hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol, iron oxide (6.25 mg only), FD&C Blue No. 2 (12.5 mg only), and carnauba wax.

CLINICAL PHARMACOLOGY

Mechanism of Action: Almotriptan binds with high affinity to 5-HT_{1D}, 5-HT_{1B}, and 5-HT_{1F} receptors. Almotriptan has weak affinity for 5-HT_{1A} and 5-HT₇ receptors, but has no significant affinity or pharmacological activity at 5-HT₂, 5-HT₃, 5-HT₄, 5-HT₆; alpha or beta adrenergic; adenosine (A₁, A₂); angiotensin (AT₁, AT₂); dopamine (D₁, D₂); endothelin (ET_A, ET_B); or tachykinin (NK₁, NK₂, NK₃) binding sites.

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 5HT_{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

General: Almotriptan is well absorbed after oral administration (absolute bioavailability about 70%) with peak plasma levels 1 to 3 hours after administration; food does not affect pharmacokinetics. Almotriptan has a mean half-life of 3 to 4 hours. It is eliminated primarily by renal excretion (about 75% of the oral dose). Almotriptan is minimally protein bound (approximately 35%) and the mean apparent volume of distribution is approximately 180 to 200 liters.

Metabolism and Excretion: Almotriptan is metabolized by one minor and two major 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.

Approximately 40% of an administered dose is 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.

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 h vs. 3.2 h) 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: The pharmacokinetics of almotriptan in pediatric patients have not been evaluated.

Gender: No significant gender differences have been observed in pharmacokinetic parameters.

Race: No significant differences have been observed in pharmacokinetic parameters between Caucasian and African-American volunteers.

Hepatic impairment: The pharmacokinetics of almotriptan have not been assessed in this population. Based on the known mechanisms of clearance of almotriptan, the maximum decrease expected in almotriptan clearance due to hepatic impairment would be 60% (see DOSAGE AND ADMINISTRATION).

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

Drug Interactions (see also PRECAUTIONS, Drug Interactions)

All drug interaction studies were performed in healthy volunteers using a single 12.5mg dose of almotriptan and multiple doses of the other drug.

Monoamine oxidase inhibitors: Coadministration of almotriptan and moclobemide (150 mg bid for 8 days) resulted in a 27% decrease in almotriptan clearance.

Propranolol: Coadministration of almotriptan and propranolol (80 mg bid for 7 days) resulted in no significant changes in the pharmacokinetics of almotriptan.

Selective serotonin reuptake inhibitors: Coadministration of almotriptan and fluoxetine (60mg daily for 8 days), a potent inhibitor of CYP4502D6, had no effect on almotriptan clearance, but maximal concentrations of almotriptan were increased 18%. This difference is not clinically significant.

Verapamil: Coadministration of almotriptan and verapamil (120mg sustained release tablets bid for 7 days), an inhibitor of CYP4503A4, 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.

Ketoconazole and other potent CYP3A4 inhibitors: Coadministration of almotriptan and the potent CYP3A4 inhibitor ketoconazole (400 mg qd for 3 days) resulted in an approximately 60% increase in the area under the plasma concentration-time curve and maximal plasma concentrations of almotriptan. Although the interaction between almotriptan and other potent CYP3A4 inhibitors (eg, itraconazole, ritonavir, and erythromycin) has not been studied, increased exposures to almotriptan may be expected when almotriptan is used concomitantly with these medications.

CLINICAL STUDIES

The efficacy of AXERT Tablets was established in 3 multi-center, randomized, double-blind, placebo-controlled European trials. Patients enrolled in these studies were primarily female (86%) and Caucasian (more than 98%), with a mean age of 41 years (range of 18 to 72). Patients were instructed to treat a moderate to severe migraine headache. Two hours after taking one dose of study medication, patients evaluated their headache pain. If the pain had not decreased in severity to mild or to no pain, the patient was allowed to take an escape medication. If the pain had decreased to mild or to no pain at 2 hours but subsequently increased in severity between 2 and 24 hours, it was considered a relapse and the patient was instructed to take a second dose of study medication. Associated symptoms of nausea, vomiting, photophobia, and phonophobia were also evaluated.

In these studies, the percentage of patients achieving a response (mild or no pain) 2 hours after treatment was significantly greater in patients who received either AXERT 6.25 mg or 12.5 mg, compared with those who received placebo. A higher percentage of patients reported pain relief after treatment with the 12.5-mg dose than with the 6.25-mg dose. Doses greater than 12.5 mg did not lead to significantly better response. These results are summarized in Table 1.

Table 1. Response Rates 2 Hours Following Treatment of Initial Headache

	Placebo	AXERT 6.25 mg	AXERT 12.5 mg
Study 1	33.8% (N= 80)	55.4% (N= 166)	58.5% [†] (N= 164)
Study 2	40.0% (N= 95)	---	57.1% [‡] (N=175)
Study 3	33.0% (N= 176)	55.6% [†] (N= 360)	64.9% [†] (N= 370)

* p value 0.002 in comparison with placebo
 † p value <0.001 in comparison with placebo
 ‡ p value 0.008 in comparison with placebo

These results cannot be validly compared with results of anti-migraine treatments in other studies. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment responses and the timing of response may be expected to vary considerably from study to study.

The estimated probability of achieving pain relief within 2 hours following initial treatment with AXERT is shown in Figure 1.

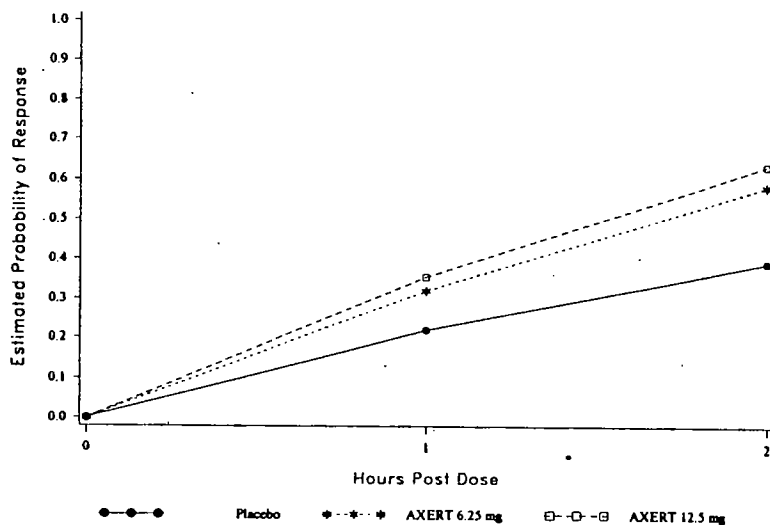


Figure 1. Estimated Probability of Achieving an Initial Headache Response (mild or no pain) in 2 Hours

This Kaplan-Meier plot is based on data obtained in the three placebo-controlled clinical trials that provided evidence of efficacy (Studies 1, 2, and 3). Patients not achieving pain relief by 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia, phonophobia, nausea, and vomiting at baseline, there was a decreased incidence of these symptoms following administration of AXERT compared with placebo.

Two to 24 hours following the initial dose of study medication, patients were allowed to take an escape medication or a second dose of study medication for pain response. The estimated probability of patients taking escape medication or a second dose of study medication over the 24 hours following the initial dose of study medication is shown in Figure 2.

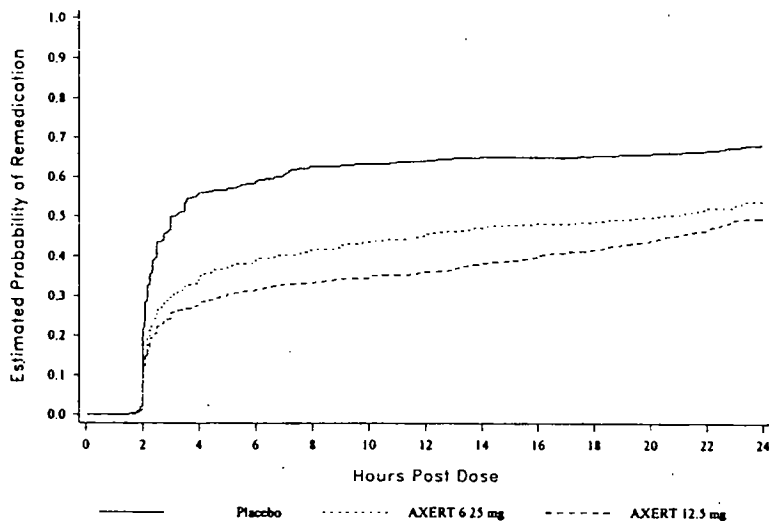


Figure 2. Estimated Probability of Patients Taking Escape Medication or a Second Dose of Study Medication Over the 24 Hours Following the Initial Dose of Study Treatment

This Kaplan-Meier plot is based on data obtained in the three placebo-controlled trials that provided evidence of efficacy (Studies 1, 2, and 3). Patients not using additional treatment were censored at 24 hours. Remedication was not allowed within 2 hours after the initial dose of AXERT.

The efficacy of AXERT was unaffected by the presence of aura; by gender, weight, or age of the patient; or by concomitant use of common migraine prophylactic drugs (eg, beta-blockers, calcium channel blockers, tricyclic antidepressants), or oral contraceptives. There were insufficient data to assess the effect of race on efficacy.

INDICATIONS AND USAGE

AXERT Tablets are indicated for the acute treatment of migraine with or without aura in adults.

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

CONTRAINDICATIONS

AXERT Tablets should not be given to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia), 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 (see WARNINGS).

Because AXERT may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

AXERT should not be administered within 24 hours of treatment with another 5-HT₁ agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

AXERT should not be given to patients with hemiplegic or basilar migraine.

AXERT is contraindicated in patients who are hypersensitive to almotriptan or any of its ingredients.

WARNINGS

AXERT Tablets 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, AXERT should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that 5-HT₁ agonists (including AXERT) not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (eg, 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 diseases or predisposition to coronary artery vasospasm is modest at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiogram (ECG), or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, AXERT should not be administered (see CONTRAINDICATIONS). 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 AXERT 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 an ECG during the interval immediately following the first use of AXERT in a patient with risk factors.

It is recommended that patients who are intermittent long-term users of AXERT 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 AXERT.

Cardiac Events and Fatalities Associated with 5-HT₁ 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-HT₁ agonists. Considering the extent of use of 5-HT₁ agonists in patients with migraine, the incidence of these events is extremely low. Among the 3865 subjects/patients who received AXERT in premarketing clinical trials, one patient was hospitalized for observation after a scheduled 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 it was also found 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.

Cerebrovascular Events and Fatalities with 5-HT₁ Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with other 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 (eg, stroke, hemorrhage, transient ischemic attack).

Other Vasospasm-Related Events: 5-HT₁ 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-HT₁ agonists.

Increases in Blood Pressure: Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension treated with other 5-HT₁ agonists. AXERT is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). In volunteers, small increases in mean systolic and diastolic blood pressure relative to placebo were seen over the first 4 hours after administration of 12.5 mg of almotriptan (0.21 and 1.35 mm Hg, respectively). The effect of almotriptan on blood pressure was also assessed

in patients with hypertension controlled by medication. In this population, mean increases in systolic and diastolic blood pressure relative to placebo over the first 4 hours after administration of 12.5 mg of almotriptan were 4.87 and 0.26 mm Hg, respectively. The slight increases in blood pressure in both volunteers and controlled hypertensive patients were not considered clinically significant.

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT₁ agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

General: As with other 5-HT_{1B/1D} agonists, sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw have been reported after treatment with AXERT Tablets. These events have not been associated with arrhythmias or ischemic ECG changes in clinical trials. 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 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. Similarly, 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-HT₁ agonist are candidates for further evaluation (see WARNINGS).

AXERT should also 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 (see CLINICAL PHARMACOLOGY, Special Populations).

For a given attack, if a patient does not respond to the first dose of AXERT, the diagnosis of migraine headache should be reconsidered before the administration of a second dose.

Binding to Melanin-Containing Tissues: When pigmented rats were given a single oral dose of 5 mg/kg of radiolabeled 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 the melanin of the eye. Because almotriptan could accumulate in melanin-rich tissues over time, there is the possibility that it could cause toxicity in these tissues over 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 systemic exposure [plasma AUC] to parent drug approximately 20 times that in humans receiving the maximum recommended daily dose of 25 mg). 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, 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 in the affected dog at 12.5 mg/kg/day after a 4-week drug-free period. 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 daily dose of 25 mg. A no-effect dose was not established.

Information for Patients: See PATIENT INFORMATION at the end of this labeling for the text of the separate leaflet provided for patients.

Laboratory Tests: No specific laboratory tests are recommended for monitoring patients.

Drug Interactions (see also CLINICAL PHARMACOLOGY, Drug Interactions)

Ergot-containing drugs: These 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 AXERT within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

Monoamine oxidase inhibitors: Coadministration of moclobemide resulted in a 27% decrease in almotriptan clearance and

an increase in C_{max} of approximately 6%. No dose adjustment is necessary.

Other 5-HT_{1B/1D} agonists: Concomitant use of other 5-HT_{1B/1D} agonists within 24 hours of treatment with AXERT is contraindicated (see CONTRAINDICATIONS).

Propranolol: The pharmacokinetics of almotriptan were not affected by coadministration of propranolol.

Selective serotonin reuptake inhibitors (SSRIs): SSRIs (eg, fluoxetine, fluvoxamine, paroxetine, sertraline) have been rarely reported to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT₁ agonists. If concomitant treatment with AXERT and an SSRI is clinically warranted, appropriate observation of the patient is advised.

Verapamil: Coadministration of almotriptan and verapamil resulted in a 24% increase in plasma concentrations of almotriptan. No dose adjustment is necessary.

Ketoconazole and other potent CYP3A4 inhibitors: Coadministration of almotriptan and the potent CYP3A4 inhibitor ketoconazole (400 mg qd for 3 days) resulted in an approximately 60% increase in the area under the plasma concentration-time curve and maximal plasma concentrations of almotriptan. Although the interaction between almotriptan and other potent CYP3A4 inhibitors (eg, itraconazole, ritonavir, and erythromycin) has not been studied, increased exposures to almotriptan may be expected when almotriptan is used concomitantly with these medications.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: The carcinogenic potential of almotriptan was evaluated by oral gavage for up to 103 weeks in mice at doses up to 250 mg/kg/day and in rats for up to 104 weeks at doses up to 75 mg/kg/day. These doses were associated with plasma exposures (AUC) to parent drug that were approximately 40 and 78 times, in mice and rats respectively, the plasma AUC observed in humans receiving the maximum recommended daily dose (MRDD) of 25 mg. Because of high mortality rates in both studies, which reached statistical significance in high dose female mice, all female rats, all male mice, and high dose female mice were terminated between weeks 96 and 98. There was no increase in tumors related to almotriptan administration.

Mutagenesis: Almotriptan was not mutagenic, with or without metabolic activation, in two gene mutation assays, the Ames test and the *in vitro* thymidine locus mouse lymphoma assay. Almotriptan was not clastogenic in an *in vivo* mouse micronucleus assay. Almotriptan produced an equivocal weakly positive response in *in vitro* cytogenetics assays in human lymphocytes.

Impairment of fertility: When female rats received almotriptan by oral gavage prior to and during mating and up to implantation at doses of 25, 100, and 400 mg/kg/day, prolongation of the estrous cycle was observed at a dose of 100 mg/kg/day (40 times the maximum recommended daily dose [MRDD] of 25 mg on a mg/m² basis). No effects on fertility were noted in female rats at 25 mg/kg/day (approximately 10 times the MRDD on a mg/m² basis).

Pregnancy: Pregnancy Category C: When almotriptan was administered by oral gavage to pregnant rats throughout the period of organogenesis at doses of 125, 250, 500, and 1000 mg/kg/day, an increase in embryoletality was seen at the highest dose (maternal exposure, based on plasma AUC of parent drug, was approximately 958 times the human exposure at the maximum recommended daily dose [MRDD] of 25 mg). Increased incidences of fetal skeletal variations (decreased ossification) were noted at doses greater than 125 mg/kg/day (maternal exposure 80 times human exposure at MRDD). Similar studies in rabbits conducted with almotriptan at doses of 5, 20, and 60 mg/kg/day demonstrated increases in embryoletality at the high dose (50 times the MRDD on a mg/m² basis). When almotriptan was administered to rats throughout the periods of gestation and lactation at doses of 25, 100, and 400 mg/kg/day, gestation length was increased and litter size and offspring body weight were decreased at the high dose (160 times the MRDD on a mg/m² basis). The decrease in pup weight persisted throughout lactation. The no-observed-effect level in this study was 100 mg/kg/day (40 times the MRDD on a mg/m² basis).

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

Nursing mothers: It is not known whether almotriptan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AXERT is administered to a nursing woman. Lactating rats dosed with almotriptan had milk levels equivalent to maternal plasma levels at 0.5 hours and 7 times higher than plasma levels at 6 hours after dosing.

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

Postmarketing experience with other triptans include a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults. The long-term safety of almotriptan in pediatric patients has not been studied.

Geriatric Use: Clinical studies of AXERT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Clearance of almotriptan was lower in elderly volunteers than in younger individuals but there were no observed differences in the safety and tolerability between the two populations (see CLINICAL PHARMACOLOGY, Special Populations). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. The recommended dose of AXERT for elderly patients with normal renal function for their age is the same as that recommended for younger adults.

ADVERSE REACTIONS

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 vasospasms, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Incidence in Controlled Clinical Trials: Adverse events were assessed in controlled clinical trials that included 1840 patients who received one or two doses of AXERT Tablets and 386 patients who received placebo.

The most common adverse events during treatment with AXERT were nausea, somnolence, headache, paresthesia, and dry mouth. In long-term open-label studies where patients were allowed to treat multiple attacks for up to one year, 5% (63 out of 1347 patients) withdrew due to adverse experiences.

Table 2 lists the adverse events that occurred in at least 1% of the patients treated with AXERT, and at an incidence greater than in patients treated with placebo, regardless of drug relationship. These events reflect experience gained under closely 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 behavior, and the kinds of patients treated may differ.

Table 2. Incidence of Adverse Events in Controlled Clinical Trials (Reported in at Least 1% of Patients Treated with AXERT, and at an Incidence Greater than Placebo)

Adverse Event	Percent of Patients Reporting the Event		
	AXERT 6.25 mg (n=527)	AXERT 12.5 mg (n=1313)	Placebo (n=386)

NDA 21-001
AXERT™ Tablets
Package Insert
5/4/01

Digestive Nausea Dry Mouth	1 1	2 1	1 0.5
Nervous Paresthesia	1	1	0.5

AXERT is generally well tolerated. Most adverse events were mild in intensity and were transient, and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, age, presence of aura, or use of prophylactic medications or oral contraceptives. There were insufficient data to assess the effect of race on the incidence of adverse events.

Other Events: In this section, the frequencies of less commonly reported adverse events are presented. However, the role of AXERT in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used AXERT in controlled clinical trials and reported an event, divided by the total number of patients exposed to AXERT in these studies. All reported events are included, except the ones already listed in the previous table, those unlikely to be drug-related, and those poorly characterized. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; and rare adverse events are those occurring in fewer than 1/1000 patients.

Body: Frequent was headache. Infrequent were abdominal cramp or pain, asthenia, chills, back pain, chest pain, neck pain, fatigue, and rigid neck. Rare were fever and photosensitivity reaction.

Cardiovascular: Infrequent were vasodilation, palpitations, and tachycardia. Rare were hypertension, and syncope.

Digestive: Infrequent were diarrhea, vomiting, and dyspepsia. Rare were colitis, gastritis, gastroenteritis, esophageal reflux, increased thirst, and increased salivation.

Metabolic: Infrequent were hyperglycemia and increased serum creatine phosphokinase. Rare were increased gamma glutamyl transpeptidase and hypercholesteremia.

Musculoskeletal: Infrequent were myalgia and muscular weakness. Rare were arthralgia, arthritis, and myopathy.

Nervous: Frequent were dizziness and somnolence. Infrequent were tremor, vertigo, anxiety, hypesthesia, restlessness, CNS stimulation, insomnia, and shakiness. Rare were change in dreams, impaired concentration, abnormal coordination, depressive symptoms, euphoria, hyperreflexia, hypertonia, nervousness, neuropathy, nightmares, and nystagmus.

Respiratory: Infrequent were pharyngitis, rhinitis, dyspnea, laryngismus, sinusitis, bronchitis, and epistaxis. Rare were hyperventilation, laryngitis, and sneezing.

Skin: Infrequent were diaphoresis, dermatitis, erythema, pruritus, and rash.

Special Senses: Infrequent were ear pain, conjunctivitis, eye irritation, hyperacusis, and taste alteration. Rare were diplopia, dry eyes, eye pain, otitis media, parosmia, scotoma, and tinnitus.

Urogenital: Infrequent was dysmenorrhea.

DRUG ABUSE AND DEPENDENCE

Although the abuse potential of AXERT Tablets has not been specifically assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received AXERT in clinical trials or their extensions. The 5-HT_{1B/1D} agonists, as a class, have not been associated with drug abuse.

OVERDOSAGE

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 AXERT Tablets, 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 5-HT agonists, hypertension or other more serious cardiovascular symptoms could occur after overdose. Gastrointestinal decontamination (ie, gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with AXERT. 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.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 6.25 mg and 12.5 mg of AXERT Tablets were effective for the acute treatment of migraines in adults, with the 12.5-mg dose tending to be a more effective dose (see CLINICAL STUDIES). Individuals may vary in response to doses of AXERT. The choice of dose should therefore be made on an individual basis.

If the headache returns, the dose may be repeated after 2 hours, but no more than two doses should be given within a 24-hour period. Controlled trials have not adequately established the effectiveness of a second dose if the initial dose is ineffective.

The safety of treating an average of more than four headaches in a 30-day period has not been established.

Hepatic impairment: The pharmacokinetics of almotriptan have not been assessed in this population. The maximum decrease expected in the clearance of almotriptan due to hepatic impairment is 60%. Therefore, the maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg should be used (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Renal impairment: In patients with severe renal impairment, the clearance of almotriptan was decreased. Therefore, the maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg should be used (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

NDA 21-001
AXERT™ Tablets
Package Insert
5/4/01

HOW SUPPLIED

AXERT Tablets are available as follows:

6.25 mg: white, circular, biconvex tablet, printed in red with the code 2080.
Unit Dose (aluminum blister pack)
6 tablets NDC 0009-5141-02

12.5 mg: white, circular, biconvex tablet, printed in blue with a stylized A.
Unit Dose (aluminum blister pack)
6 tablets NDC 0009-4618-04

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Rx only

US Patent No. 5,565,447

Manufactured for: Pharmacia & Upjohn Company
 Kalamazoo, MI 49001, USA

By: Atlantic Pharmaceutical Services
 Owings Mills, MD 21117, USA

Licensed from: Almirall Prodesfarma

[Date]

[Copy code]

PATIENT INFORMATION

The following wording is contained in a separate leaflet provided for patients.

Patient information about

AXERT™ Tablets

Generic name: almotriptan malate tablets

Please read this information before you start taking AXERT Tablets. Also, read this leaflet each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss AXERT when you start taking your medication and at regular checkups.

What is AXERT and what is it used for?

AXERT is a medication used to treat migraine attacks in adults. AXERT is a member of a class of drugs called selective serotonin receptor agonists.

Use AXERT only for a migraine attack. Do not use AXERT to treat headaches that might be caused by other conditions. Tell your doctor about your symptoms. Your doctor will decide if you have migraine.

There is more information about migraine at the end of this leaflet.

Who should not take AXERT? *

Do not take AXERT if you:

- have ever had heart disease.
- have uncontrolled high blood pressure.
- have hemiplegic or basilar migraine. If you are not sure, ask your doctor.
- have taken another serotonin receptor agonist in the last 24 hours. These include naratriptan (AMERGE™), rizatriptan (MAXALT®), sumatriptan (IMITREX®), or zolmitriptan (ZOMIG™).
- have taken ergotamine-type medicines in the last 24 hours. These include ergotamine (BELLERGAL-S®, CAFERGOT®, ERGOMAR®, WIGRAINE®), dihydro-ergotamine (D.H.E. 45®), or methysergide (SANSERT®).
- had an allergic reaction to AXERT or any of its ingredients. The active ingredient is almotriptan malate. As your doctor or pharmacist about inactive ingredients.

Tell your doctor if you take

- monoamine oxidase (MAO) inhibitors, such as phenelzine sulfate (NARDIL®) or tranylcypromine sulfate (PARNATE®) for depression or another condition, or if it has been less than two weeks since you stopped taking a MAO inhibitor.
- ketoconazole (NIZORAL®), itraconazole (SPORANOX®), ritonavir (NORVIR®), or erythromycin (EMYCIN®), or if it has been less than one week since you stopped taking one of these drugs.

These medicines may affect how AXERT works, or AXERT may affect how these medicines work.

To help your doctor decide if AXERT is right for you or if you need to be checked while taking AXERT, tell your doctor about any

- past or present medical problems
- past or present high blood pressure, chest pain, shortness of breath, or heart disease
- liver or kidney problems
- risk factors for heart disease, such as:
 - high blood pressure
 - diabetes
 - high cholesterol

* The brands listed are the trademarks of their respective owners and are not trademarks of Pharmacia & Upjohn, Inc.

- overweight
- smoking
- family members with heart disease
- You are past menopause
- You are a male over 40 years old
- plans to become pregnant, or if you are pregnant, might be pregnant, or do not use effective birth control
- plans to breast-feed, or if you are already breast-feeding
- medicines you are take or plan to take, including prescription and non-prescription medicines and herbal supplements. Be sure to include medicines you normally take for a migraine.

How should I take AXERT?

- When you have a migraine headache, take your medicine as directed by your doctor.
- If your headache comes back after your first dose, you may take a second dose 2 hours or more after the first dose. If your pain continues after the first dose, do not take a second dose without first checking with your doctor.
- Do not take more than two AXERT tablets in a 24-hour period.
- If you take too much medicine, contact your doctor, hospital emergency department, or poison control center right away.

What should I avoid while taking AXERT?

Check with your doctor before you take any new medicines, including prescription and non-prescription medicines and supplements. There are some medicines that you should not take during the period 24 hours before and 24 hours after taking AXERT. Some of them are listed in the section "Who should not take AXERT?"

What are the possible side effects of AXERT?

AXERT is generally well tolerated. The side effects are usually mild and do not last long. The following is not a complete list of side effects. Ask your doctor to tell you about the other side effects.

The most common side effects are

- Nausea
- Sleepiness
- Tingling or burning feeling (paresthesia)
- Headache
- Dry mouth

If you experience sleepiness, you should evaluate your ability to perform complex tasks such as driving or operating heavy machinery.

Tell your doctor about any other symptoms that you develop while taking AXERT. If the symptoms continue or worsen, get medical help right away. Also, tell your doctor if you develop a rash or itching after taking AXERT. You may be allergic to the medicine.

In very rare cases, patients taking this class of medicines experience serious heart problems, stroke, or increased blood pressure. Extremely rarely, patients have died. Therefore, tell your doctor right away if you feel tightness, pain, pressure or heaviness in your chest, throat, neck, or jaw after taking AXERT. Do not take AXERT again until your doctor has checked you.

What is migraine and how does it differ from other headaches?

Migraine is an intense, throbbing, typically one-sided headache. It often includes nausea, vomiting, sensitivity to light, and sensitivity to sound. The pain and symptoms from a migraine headache may be worse than the pain and symptoms of a common headache.

Some people have visual symptoms before the headache, such as flashing lights or wavy lines, called an aura.

Migraine attacks typically last for hours or, rarely, for more than a day. They can return often. The strength and frequency of migraine attacks may vary.

Based on your symptoms, your doctor will decide whether you have migraine.

Migraine headaches tend to occur in members of the same family. Both men and women get migraine, but it is more common in women.

What may trigger a migraine attack?

Certain things may trigger migraine attacks in some people. Some of these triggers are:

- Certain foods or drinks, such as cheese, chocolate, citrus fruit (oranges, grapefruit, lemons, lime, and others), caffeine, and alcohol
- Stress
- Change in behavior, such as too much or too little sleep, missing a meal, or a change in diet
- Hormone changes in women, such as during monthly menstrual periods

You may be able to prevent migraine attacks or make them come less often if you understand what triggers your attacks. Keeping a headache diary may help you identify and monitor the possible triggers that cause your migraine. Once you identify the triggers, you and your doctor can change your lifestyle to avoid those triggers.

How does AXERT work during a migraine attack?

Treatment with AXERT:

- Reduces swelling of blood vessels surrounding the brain. This swelling is associated with the headache pain of a migraine attack.
- Blocks the release of substances from nerve endings that cause more pain and other symptoms of migraine.
- Interrupts the sending of specific pain signals to your brain.

It is thought that each of these actions contributes to relief of your symptoms by AXERT.

How should I store AXERT?

Keep your medicine in a safe place where children cannot reach it. It may be harmful to children. Store your medicine away from heat, light, or moisture, at a controlled room temperature. If your medicine has expired, throw it away as instructed. If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to do so. Throw away your medicine as instructed. Be sure that discarded tablets are out of the reach of children.

General advice about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use AXERT for a condition for which it was not prescribed. Do not give AXERT to other people, even if they have the same symptoms you have. People may be harmed if they take medicines that have not been prescribed to them.

This leaflet provides a summary of information about AXERT. If you have any questions or concerns about either AXERT or migraines, talk to your doctor. In addition, talk to your pharmacist or other health care provider.