

# NEW DRUG UPDATE

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## Keppra® (levetiracetam)

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### Introduction

Keppra® [levetiracetam (le-vi-tir-AS-i-tam)] is a new antiepileptic agent that was FDA approved in November 1999. Levetiracetam is indicated as adjunctive therapy for the treatment of partial seizures (with or without secondary generalization) in adults with epilepsy.

### Therapeutic Recommendation

Levetiracetam is an effective anti-seizure agent when used for the treatment of partial seizures with or without secondary generalization. Levetiracetam has not been compared directly with other anti-epileptic drugs (AEDs) and is postulated to have a mechanism of action unrelated to any known mechanism involving inhibitory/excitatory processes. In three clinical trials, levetiracetam was proven to have good anticonvulsant efficacy. When randomized with placebo, levetiracetam was found to have tolerability similar to placebo. Levetiracetam is metabolized by hydrolysis

and thus, is neither an inhibitor nor a substrate for any human cytochrome P450 isoenzymes. Approximately 66% of an oral dose of levetiracetam is excreted unchanged in the urine while its inactive metabolites are secreted in the urine. Therefore, a dosage adjustment may be necessary based on a patient's estimated creatinine clearance. In clinical trials, levetiracetam was found to have no clinically significant interactions with existing AEDs, digoxin, warfarin or oral contraceptives. Levetiracetam is, however, more expensive than most other AEDs. Levetiracetam has a place in the treatment of refractory partial seizures. Clinical studies have demonstrated levetiracetam's efficacy at controlling refractory seizures when added to existing AEDs. The addition of levetiracetam should be considered in those patients already on an anti-epileptic regimen but experiencing "refractory" seizures. These patients should be evaluated for poor renal function in order to initiate the appropriate dose. Since levetiracetam exhibits no known drug interactions with existing AEDs, it may be an optimal add-on agent in some instances.

### Dosing and Administration

Levetiracetam is available as 250 mg, 500 mg, and 750 mg tablets for oral administration. All three strengths are oval, film coated and scored.

**Inside  
This  
Issue:**

▶ Keppra® (levetiracetam)

▶ Axert® (almotriptan)

Their colors are blue, yellow and orange respectively. It is recommended that treatment be initiated with a dose of 1000 mg/day, given twice daily (e.g., 500 mg bid). The dose may then be increased by 1000 mg every 2 to 4 weeks to a maximum of 3000 mg/day given twice daily. All doses may be taken with or without food.

**Cost Comparison**

Medication/Dose	Cost*		
	KMart	Rite Aid	CVS
Trileptal® (Oxcarbazepine) 600 mg bid	188.97	211.99	211.99
Dilantin® (Phenytoin) 100 mg tid	23.49 **16.99	30.99 **29.99	33.29 **22.69
Depakote® (Divalproex Na+) 500 mg bid	99.79	111.99	107.99
Keppra® (Levetiracetam) 500 mg bid	108.97	119.99	126.99

\*Prices represent cost to the patient for a thirty-day supply  
\*\*Reflects generic price

**General Precautions**

Withdrawal of levetiracetam should be a gradual process in order to minimize the potential for seizure occurrence. Clinical studies have

shown minor, yet statistically significant, decreases in total mean RBC count, mean hemoglobin, and mean hematocrit in patients receiving levetiracetam versus placebo.

**Contraindications**

Levetiracetam is contraindicated in patients with a known hypersensitivity to levetiracetam or any of its components

**Special populations**

**Hepatic Impairment:** No dosage adjustment is necessary in the presence of mild to moderate hepatic impairment. In patients with severe hepatic impairment, total body clearance was decreased by 50% versus that of normal subjects. However, impaired renal clearance accounted for the majority of the decrease.

**Renal Impairment:** Renal clearance is the major route of elimination of levetiracetam with approximately two-thirds of an oral dose being recovered unchanged in the urine. Therefore, levetiracetam therapy must be individualized according to a patient's renal function. Recommended renal dose adjustments are as follows:

Group	Creatinine Clearance		Dosage (mg)	Frequency
	(mL/min)			
Normal	>80		500 to 1500	q 12h
Mild	50-80		500 to 1000	q 12h
Moderate	30-50		250 to 750	q 12h
Severe	<30		250 to 500	q 12h
ESRD (on dialysis)	-----		500 to 1000	q 24h

When initiating therapy in a patient with end-stage renal disease (ESRD), it is recommended to give a 750 mg loading dose of levetiracetam. Following dialysis, a 250 to 500 mg supplemental dose is recommended.

**Pediatric Use:** Levetiracetam is not indicated for use in patients younger than 16 years of age.

**Geriatric Use:** Caution is advised when prescribing levetiracetam in the elderly population. Due to age related decreases in creatinine clearance, dosage adjustments may be necessary.

**Pregnancy:** Levetiracetam is a **Pregnancy Category C** agent. Administration of levetiracetam in animal models has shown fetal abnormalities and increased mortality. There are no



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adequate, well –controlled trials in pregnant women. Therefore, levetiracetam should only be used during pregnancy when the potential benefit outweighs any fetal risks.

**Lactation:** It is unknown whether levetiracetam is excreted in human milk. Therefore, caution should be exercised when levetiracetam is administered to nursing mothers.

### Drug Interactions

In vitro data on metabolic interactions indicate that levetiracetam is unlikely to produce, or be subject to interactions. Levetiracetam and its major metabolite are neither inhibitors of nor substrates for human cytochrome P450 isoenzymes, epoxide hydrolase or UDP-glucuronidation enzymes. Levetiracetam is largely unbound to plasma proteins (<10%). During placebo-controlled clinical studies, potential drug interactions between levetiracetam and other AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) were evaluated by monitoring serum concentrations of levetiracetam and the AEDs. These data indicated that neither levetiracetam nor existing AEDs were influenced by the presence of each other. Clinical studies also determined that co-administration of levetiracetam with oral contraceptives, digoxin, and warfarin produced no clinically significant interactions. Probenecid was found to block renal secretion of levetiracetam's primary (inactive) metabolite. The excretion of levetiracetam itself was unaffected.

### Common Adverse Drug Reactions

In placebo-controlled studies comprised of approximately 1208 test subjects, adverse effects were more frequent with levetiracetam therapy than with placebo. The most common were asthenia (15%>9%), somnolence (15%>8%), headache (14%>13%), infection (13%>8%), dizziness (9%>4%), pain (7%>6%), pharyngitis (6%>4%), depression (4%>2%), nervousness (4%>2%), rhinitis (4%>3%) and ataxia (3%>1%).

### Pharmacology

**Mechanism of Action:** The exact mechanism of

action of levetiracetam is undefined. It is believed however that levetiracetam exerts its therapeutic effect by a mechanism unlike any existing AED. Levetiracetam appears to act via a specific binding site in the membranes of the CNS.

**Absorption/Distribution:** Levetiracetam is rapidly and nearly completely absorbed following oral administration. Peak plasma concentrations are achieved in approximately one hour following oral administration in fasted subjects. Oral bioavailability of levetiracetam tablets is 100%. Food does not affect the extent of absorption but does decrease maximum concentration by 20% and delay time to maximum concentration by 1.5 hours. Levetiracetam is minimally bound to plasma proteins (<10%). The half-life of levetiracetam is approximately 6-8 hours, therefore steady-state concentrations can be achieved in two days.

**Metabolism/Elimination:** Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is enzymatic hydrolysis, producing its major, inactive metabolite. This metabolic pathway is independent of liver cytochrome P450 isoenzymes. Levetiracetam is eliminated from systemic circulation by renal excretion. Approximately two-thirds of an oral dose is excreted as unchanged drug. No dosage adjustment is necessary in mild to moderate hepatic impairment. Levetiracetam's elimination, however, is correlated to creatinine clearance. Therefore levetiracetam therapy may require dosage adjustment based on the patient's renal status.

### Patient Information

1. Women of child bearing age should be aware that levetiracetam should be used during pregnancy only if the potential benefits outweigh the risk to the fetus. Therefore, patients should notify their physicians if they become or intend to become pregnant.
2. Levetiracetam may cause drowsiness and dizziness. Therefore patients should use caution if driving or operating machinery.
3. Caution should be used if consuming alcohol with levetiracetam due to the possibility of intensified side effects of levetiracetam (i.e., drowsiness).
4. Patients should take levetiracetam only as directed by their physician.

**References:**

1. Dooley M, Plosker G. Levetiracetam A Review of its Adjunctive Use in the Management of Partial Onset Seizures. *Drugs* 2000 Oct; 60 (4);871-893.
2. Keppra® prescribing information. UCB Pharma, Inc., Smyrna, GA, December 1999.

**Axert® (almotriptan)**

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**Introduction**

Axert® [almotriptan (al-moh-TRIP-tan)] is a selective 5-hydroxytryptamine<sub>1B/1D</sub> (5-HT<sub>1B/1D</sub>) receptor agonist. It is used for the acute treatment of migraine with or without aura in adults. The product was FDA approved on April 4, 2001.

**Therapeutic Recommendation**

**Almotriptan has similar efficacy compared to other agents in this class. However, premarketing clinical trials indicated that almotriptan might be less likely to cause chest symptoms. This may be due to almotriptan having a selective affinity for 5-HT<sub>1B/1D</sub> receptors and acting very precisely at human cranial vessels with little activity at peripheral human arteries. Despite these preliminary findings, postmarketing surveillance is still needed to confirm this potential benefit. Therefore, if a patient has significant cardiovascular disease or risk factors almotriptan should not be used.**

**Dosing and Administration**

Almotriptan is available as a 6.25 mg tablet and a 12.5 mg non-scored tablet. The recommended adult dosage is a single 6.25 mg or 12.5 mg tablet at the onset of migraine symptoms. If the migraine returns, the dose may be repeated after 2 hours, but no more than two doses should be given within a 24-hour period.

**Cost Comparison**

Medication/Dose	Cost*		
	Kroger	KMart	RiteAid
Axert® (almotriptan) 25 mg/d	102.79	91.97	113.00
Imitrex® (sumatriptan) 200 mg/d	288.69	253.79	307.99
Zomig® (zomitriptan) 5 mg/d	136.49	117.79	147.99
Maxalt® (rizatriptan) 20 mg/d	149.79	131.97	143.99
Amerge® (naratriptan) 5 mg/d	159.79	139.69	174.99

\*One month supply assuming maximum dose for 4 attacks per month

**Contraindications**

Almotriptan is contraindicated in patients with ischemic heart disease, patients with symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, uncontrolled hypertension, or other significant underlying cardiovascular disease. This is due to the fact that it may cause peripheral artery vasoconstriction. In addition, it is contraindicated in patients with hemiplegic or basilar migraines, patients with cluster headaches, and patients who are hypersensitive to almotriptan or any of its ingredients. Almotriptan is also contraindicated if patients have a hypersensitivity to almotriptan or any of its components (mannitol, cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, titanium dioxide, hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol, iron oxide (6.25 mg tablets only), FD&C blue no. 2 (12.5 mg tablets only), and carnauba wax).

**Special Populations**

Geriatrics: Age related renal dysfunction reduces renal clearance, total clearance, and amount of drug eliminated in the elderly. Therefore, almotriptan should be used cautiously in elderly patients. Dosing should begin low and titrated as needed.

Pediatrics: The pharmacokinetics in pediatric patients has not been evaluated. Children less than 18 should not use almotriptan.

**Hepatic impairment:** The pharmacokinetics in this population has not been studied. However, it is recommended that an initial 6.25 mg dose be used and the maximum daily dose should not exceed 12.5 mg.

**Renal impairment:** Almotriptan is eliminated primarily by renal excretion (~75% of the oral dose of which ~40% is excreted unchanged in the urine). In patients with severe renal dysfunction ( $Cl_{Cr} < 30$  ml/min) excretion of almotriptan is reduced. Therefore, for these patients, the maximum daily dose should not exceed 12.5 mg in a 24-hour period and a starting dose of 6.25 mg should be used.

**Pregnancy:** Almotriptan is a **Pregnancy Category C** agent. No adequate, well-controlled studies in pregnant women have been performed. Therefore, use in pregnancy should be limited to situations where benefit outweighs risk to the fetus.

**Lactation:** It is not known whether almotriptan is excreted into human milk.

### Drug Interactions

**Other 5-HT<sub>1B/1D</sub> agonists:** Concomitant use of other 5-HT<sub>1B/1D</sub> agonists within 24 hours of treatment with almotriptan is contraindicated.

**Ergotamine-containing drugs:** Ergotamines have been reported to cause prolonged vasospastic reactions. Therefore, since almotriptan also causes this reaction, ergotamines and almotriptan should not be used within 24 hours of each other.

**MAO Inhibitors:** Almotriptan partially undergoes MAO-mediated metabolism to an inactive metabolite. Therefore, concomitant use of almotriptan and MAOIs should be avoided.

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

**SSRIs:** Coadministration of almotriptan and fluoxetine (60 mg daily for 8 days), a potent inhibitor of CYP 2D6, had no effect on almotriptan clearance, but maximal concentrations of almo-

triptan were increased 18%. However, this difference was not clinically significant.

**Verapamil:** Coadministration of almotriptan and verapamil (120 mg sustained release tablets BID for 7 days), an inhibitor of CYP 3A4, 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 are considered clinically significant.

**Ketoconazole and other potent CYP 3A4 inhibitors:** Coadministration of almotriptan and the potent CYP 3A4 inhibitor ketoconazole (400mg 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 CYP 3A4 inhibitors (e.g., itraconazole, ritonavir, and erythromycin) has not been studied, increased exposures to almotriptan may be expected when almotriptan is used concomitantly with these medications.

### Common Adverse Drug Reactions

In premarketing clinical studies, adverse effects were mild and of low incidence. The most common events were dizziness, nausea and vomiting, headache, fatigue, paresthesia, and drowsiness. These were reported in fewer than 3% of patients, and the incidence and severity were not statistically different from placebo for oral doses up to 12.5 mg.

Data from premarketing clinical studies which included over 2,500 patients with migraine and over 15,000 migraine attacks indicated that oral almotriptan is well tolerated and may be associated with a substantially lower incidence of chest symptoms than sumatriptan. However, almotriptan still should not be administered to patients with significant risk factors for cardiovascular disease.

### Pharmacology

**Mechanism of Action:** Almotriptan binds with high affinity to 5-HT<sub>1D</sub>, 5-HT<sub>1B</sub>, and 5-HT<sub>1F</sub> receptors. It also has a weak affinity for 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> receptors. The current theory of migraine headaches suggest that symptoms are due to local cranial vasodilation and/or to the release of vasoactive and proinflammatory peptides from sensory nerve endings in an activated trigeminal

system. Therefore, the therapeutic activity of almotriptan in migraine can most likely be attributed to agonist effects at 5-HT<sub>1B/1D</sub> 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 thereby reducing the symptoms of a migraine.

**Absorption /Distribution:** Almotriptan is well absorbed after oral administration with an absolute bioavailability of ~70% with peak plasma levels in 1-3 hours. Food does not affect the pharmacokinetics of almotriptan. The mean half-life of it is 3-4 hours.

**Metabolism/Excretion:** One minor and two major pathways metabolize almotriptan. MAO-mediated oxidative deamination and CYP 3A4 and 2D6 mediated oxidation are the major routes of metabolism, while flavin monooxygenase is the minor route. Approximately 40% of an administered dose is excreted unchanged in the urine and approximately 13% of the dose, both unchanged and metabolized, is excreted via feces.

### Patient Information

1. Please inform your doctor if you have ever had heart disease, uncontrolled high blood pressure, hemiplegic or basilar migraine, cluster headaches, have taken another serotonin receptor agonist in the last 24 hours (e.g. Zomig®, Amerge®, Imitrex®, or Maxalt®), have taken ergotamine-type medications in the last 24 hours

(e.g. Bellergal-S®, Cafergot®, Erogomar®, or Wigraine®, DHE 45®, or Sansert®), or have had an allergic reaction to Axert® or any of its ingredients.

2. Tell your doctor if you take a MAO inhibitor (e.g. Nardil® or Parnate®) or ketoconazole (Nizoral®), itraconazole (Sporanox®), ritonavir (Norvir®), or erythromycin, or if it has been less than a week since you stopped taking one of these drugs. In addition, make sure your doctor knows all the medications you are taking, including non-prescription and herbal medications.
3. The most common side effects of almotriptan are nausea, sleepiness, tingling or burning headache, and dry mouth. Tell your doctor if you experience any of these or any other side effects while taking almotriptan. If symptoms continue or worsen, get medical attention as soon as possible.
4. In rare cases this class of medications has caused serious heart problems. Therefore, seek medical care right away if you feel tightness, pain, pressure or heaviness in your chest, throat, neck, or jaw after taking almotriptan. Do not take the medication again until you have been fully evaluated by a physician.

### References:

1. Axert® (almotriptan) prescribing information, Pharmacia Corp. Chicago, IL, May, 2001.
2. Dodick David. Oral Almotriptan in the Treatment of Migraine: Safety and Tolerability. *Headache* 2001;41:449-55.
3. Cull Robert. Almotriptan: A Balanced Approach to Migraine. *Hospital Medicine* 2001;62(2):96-100.



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