Migraine is a common condition characterized by severe headaches and accompanied by chronic head pain, nausea, vomiting, and photophobia. Migraines affect approximately 18% of women and 6% of men in the U.S. Migraines can significantly affect a person’s quality of life. Approximately 86% of women and 82% of men report some disability with each migraine attack.\(^1,2\) The loss of productivity associated with migraines is estimated to range from 6.5 to 17.2 billion dollars per year, making this condition a costly public health problem.\(^1\) Therefore, appropriate drug therapy is key to the treatment of this chronic condition.

Although the exact mechanism of migraines is still unknown, they are thought to be mediated by alterations in the activity of serotonin, 5-hydroxytryptamine (5-HT). Of the seven classes of 5-HT receptors, the 5-HT\(_{1B}\) receptor plays a key role in the pathogenesis of migraine. During a migraine attack, there are several neurological changes that take place, including neurogenic inflammation, activation of neuropeptides, and vasodilation of the meningeal vessels. The neurological changes result in the release of vasoactive neuropeptides leading to vasodilation and producing the pain of a migraine. The 5-HT\(_{1B}\) and 5-HT\(_{1D}\) receptors are two of the five 5-HT\(_1\) subtypes identified and are thought to be directly involved in the origin of migraines. The 5-HT\(_{1B}\) receptors are predominately located in the meningeal arteries and cause vasoconstriction of cranial vessels when stimulated, whereas the 5-HT\(_{1D}\) receptors, found on trigeminal nerve endings, directly inhibit the release of the proinflammatory neuropeptides when stimulated. There are currently six selective 5-HT\(_{1B/1D}\) agonists available in the U.S. and one, eletriptan (Relpax, Pfizer) currently awaiting FDA approval (Table 1).

Almotriptan (Axert, Pharmacia), a second-generation triptan, received FDA approval in May of 2001. This new triptan was developed to improve potency and selectivity for the 5-HT\(_{1B/1D}\) Receptor. Almotriptan also shows a high affinity for the 5-HT\(_{1F}\) receptor located in the brain and periphery. This is a similarity among all of the 5-HT\(_1\) agonists. As previously mentioned, almotriptan works by stimulating the 5-HT\(_{1B}\) receptors located on vascular smooth muscle, inducing vasoconstriction. Almotriptan also inhibits the release of inflammatory chemicals by stimulating the 5-HT\(_{1D}\) receptor found on nerve fibers. Although structurally related to sumatriptan, its vasoconstrictor properties in the meningeal arteries are 25 times more potent than sumatriptan.\(^2\) All the 5-HT\(_{1B/1D}\) agonists are 3,5 substituted tryptamine derivatives, except for frovatriptan, which is a carbazole derivative.

Almotriptan is indicated for the acute treatment of migraine with or without aura. Almotriptan’s safety and efficacy in other types of headaches (i.e., cluster headache), as well as prophylactic therapy in migraine has not been established.

### DOSAGES

Almotriptan is available as an oral formulation in doses of 6.25-mg and 12.5-mg tablets. The recommended dosage regimen of almotriptan is 6.25 mg or 12.5 mg at the onset of migraine, with a repeat dose in two hours if no relief is achieved (maximum daily dose is 25 mg/day). Expected decreases in the clearance of patients with hepatic and renal impairment warrant the dose to be started at 6.25 mg and not to exceed 12.5 mg/day in these patients.\(^3\) Approximately 45% of the drug is found unchanged in the urine and 13% is excreted via the fecal route.\(^3\)

### DRUG INTERACTIONS

Almotriptan has a lower incidence of drug interactions than the other triptans. Approximately 12% of the drug is metabolized by the CYP450-3A isoenzyme, with alternative pathways, including monoamine oxidase (MAO-A) oxidative deamination. Almotriptan’s plasma concentrations were shown to increase by 37% when coadministered with the monoamine oxidase inhibitor moclobemide.\(^2,3\) However, dosage adjustments are not warranted with this combination. Naratriptan (Amerge, GlaxoWellcome) is the only other triptan not contraindicated with the MAO-inhibitors.
Coadministration of almotriptan with drugs such as propranolol, verapamil and selective serotonin reuptake inhibitors (SSRIs) showed no significant differences in plasma concentrations.2,3 However, patients taking any of the SSRIs (i.e., fluoxetine, paroxetine or sertraline), should be counseled on the potential risk of serotonin syndrome (i.e., weakness, hyperreflexia, incoordination). In addition, almotriptan should not be taken within 24 hours of any other 5HT1B/1D agonist because of this potential syndrome. Coadministration of ketoconazole resulted in a 60% increase in almotriptan plasma concentrations and therefore the use of the two medications should be avoided. Other potent CYP 3A4 inhibitors (i.e., itraconazole, erythromycin, ritonavir) should be used with caution in patients taking almotriptan or any of the 5-HT1B/1D agonists.

The constrictive effects of the triptans are predominately on the meningeal vessels; however, there is still concern with coronary vasoconstriction, although to a lesser extent. Therefore, almotriptan as well as the other agents in its class, should not be given to patients with various forms of cardiovascular disease (Table 2). Patients taking almotriptan on a long-term basis who have documented cardiovascular disease (i.e., myocardial infarction or angina) or risk factors for coronary artery disease (i.e., hypertension, diabetes, obesity, dyslipidemia) should have their cardiovascular status monitored regularly and closely. Well-controlled studies of almotriptan with pregnant women are not available, therefore it should be used only when the potential benefits outweigh the potential risks to the fetus.3

PHARMACOKINETICS

Bioavailability
Although all of the triptans possess the same pharmacological actions, each has slightly different pharmacokinetic characteristics, resulting in differences in onset and duration of action. This variation allows the prescriber to choose the most appropriate drug to optimize a patient’s therapy (Table 3). Compared to the other triptans, almotriptan has the highest oral bioavailability with a comparable onset and duration of action.

Side Effects
There are limited studies comparing almotriptan to the newer triptans. Many of the head-to-head trials use sumatriptan as the standard comparison drug. Overall, fewer side effects have been reported in patients taking almotriptan than

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**Table 1 Available 5-HT1B/1D Agonists5,12**

<table>
<thead>
<tr>
<th>5-HT1B/1D Agonist</th>
<th>Dosage Form</th>
<th>Price (number of tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>5-, 20-mg nasal spray</td>
<td>$118.08(6), $120.60(6)</td>
</tr>
<tr>
<td>(Imitrex, GlaxoSmithKline)</td>
<td>6 mg/0.5 ml sc injection</td>
<td>$242.43 (5 vials)</td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>$137.65(9)</td>
</tr>
<tr>
<td></td>
<td>50 mg, 100 mg</td>
<td>$134.70(9)</td>
</tr>
<tr>
<td>Zolmitriptan (Zomig, AstraZeneca)</td>
<td>2.5 mg</td>
<td>$80.64(6)</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>$133.30(9)</td>
</tr>
<tr>
<td>Zolmitriptan ZMT</td>
<td>5 mg</td>
<td>$142.18(9)</td>
</tr>
<tr>
<td>Naratriptan (Amerge, GlaxoWellcome)</td>
<td>1, 2.5 mg</td>
<td>$146.61(9)</td>
</tr>
<tr>
<td>Rizatriptan (Maxalt, Merck)</td>
<td>5, 10 mg</td>
<td>$91.46(6)</td>
</tr>
<tr>
<td>Rizatriptan MLT</td>
<td>5, 10 mg</td>
<td>$91.46(9)</td>
</tr>
<tr>
<td>Almotriptan (Axert, Pharmacia)</td>
<td>6.25, 12.5 mg</td>
<td>$65.93(6)</td>
</tr>
<tr>
<td>Froxatriptan (Frova, Elan)</td>
<td>2.5 mg</td>
<td>Not available</td>
</tr>
</tbody>
</table>

**Table 2 Summary of Contraindications and Warnings2,5**

- Patients with uncontrolled hypertension
- Patients with ischemic heart disease (angina pectoris, history of myocardial infarction or documented silent ischemia)
- Patients with coronary artery vasospasm (Prinzmetal’s angina)
- Not to be administered within 24 hours of another 5-HT1B/1D agonist or ergotamine-containing or ergotamine-like medication (i.e., dihydroergotamine, methysergide)
- Patients diagnosed with hemiplegic or basilar migraine

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**continued on page 88**
sumatriptan (Imitrex, GlaxoSmithKline). Spierings and colleagues evaluated almotriptan compared to oral sumatriptan in the abortive treatment of migraine. The authors observed a significant difference between the reported adverse effects, specifically chest pain, of the two groups in favor of the almotriptan-treated group (0.3 vs. 2.2; \(P=0.004\)). Other treatment-related adverse events (i.e., diarrhea, nausea, dizziness, and somnolence) occurred one-third less often in the almotriptan-treated group than in patients receiving sumatriptan (\(P=0.001\)). There were no significant differences between the two groups with respect to cardiovascular adverse events (i.e., palpitations, syncope, tachycardia, and abnormal cardiac rhythm) (\(P=0.06\)).

**CLINICAL TRIALS**

It is essential to recognize the clinical endpoints that are assessed in migraine drug trials when evaluating the medical literature and determining which triptan to utilize (Table 4). According to the International Headache Society, the recommended primary efficacy endpoint in migraine studies is being pain-free at two hours.\(^6,7\) Clinical endpoints commonly\(^7\) overlooked include improvement of a patient’s quality of life and functional status.

Although these study endpoints are subjective, they are essential components to migraine research. A patient’s quality of life can be disrupted as a result of a migraine episode. Approximately 92% of all migraineurs have a disruption of normal activities during an attack and about 50% are forced to discontinue their daily activities.\(^8\) In a randomized multicentered study by Colman et al., almotriptan was compared to sumatriptan with respect to treatment satisfaction, functional status, and health-related quality-of-life issues.\(^7\) The study used a six-item survey to address the degree of quality-of-life issues (i.e., relief of symptoms, side effects experienced, duration of migraine relief, etc). Overall, there was no significant difference between the two groups with respect to pain relief at 48 hours (\(P=0.67\)). However, the almotriptan group had a higher rate of satisfaction and tolerability of side effects than sumatriptan (81.29 vs. 77.46, respectively; \(P=0.016\)). Improvement in functional status and quality of life was comparable among the two groups at 24 hours. The study con-
cluded that although there were no differences in the time to achieve pain relief, the side effect profile of almotriptan was more desirable than sumatriptan. These results might help inform prescribers about potential benefits of almotriptan in terms of patient satisfaction.

In the previously mentioned study, Spierings et al. observed similar results between almotriptan and sumatriptan. At two hours, 58% of patients in the almotriptan-treated group and 57% of patients receiving sumatriptan reported pain relief. However, more patients were pain-free at two hours in the group receiving sumatriptan (25% vs. 18%; P=0.005).4,7 There were no significant differences between the two groups in the number of patients reporting headache recurrence within 24 hours (27% in the almotriptan group vs. 24% of those receiving sumatriptan). As reported in previously mentioned studies, the incidence of adverse effects was significantly lower in patients taking almotriptan (9% vs. 16%; P=0.001).

There are several trials that have studied the safety and efficacy of almotriptan compared to placebo. Cabarrocas et al. performed a one-year open-label study with almotriptan 12.5 mg.9 The study objectives included assessment of safety and efficacy of a single dose of almotriptan in the treatment of migraine attacks in patients with a history of migraine for one year. Additional assessments included a written survey, which evaluated the presence of symptoms (i.e., pain intensity), the need for rescue medications (i.e., nonsteroidal anti-inflammatory drugs, analgesics, combination analgesics with or without opiate narcotics) and the time to next migraine. Results showed that of the 747 patients receiving the study drug, 43% of patients experienced pain relief after one hour of their first attack and 73% experienced relief at two hours. Back pain was the most common adverse event, reported in 51% of patients. Only 18 patients (7%) withdrew from the study because of adverse events. These results were shown to be similar to other placebo-controlled studies.

The efficacy and tolerability of almotriptan at varying doses in the treatment of migraine was assessed by Dahof et al.10 This double-blind controlled study randomized patients into one of four dosage regimens of almotriptan (i.e., 2, 6.25, 12.5 or 25
mg) as compared to placebo. Primary study endpoints were defined as a decrease in the severity of migraine pain two hours after treatment. Secondary endpoints assessed the use of escape medications, relief of associated migraine symptoms, and incidence of recurrence. The study found a dose-dependent response with respect to the number of patients who did not use escape medications within two hours after treatment. The 2-mg dose was comparable to that of placebo and the 25-mg dose showed no additional benefit over 12.5 mg. The incidence of adverse events was similar between the 12.5-mg dose and placebo, whereas there was an increase in adverse events (i.e., gastrointestinal and nervous-system-related) reported with the 25-mg dosage.

Ferrari and colleagues reviewed 53 clinical trials, including 24,000 patients, comparing all available triptans. The goal of this meta-analysis was to assist physicians in prescribing the most appropriate medication in the class. Primary outcomes were measurements of complete migraine relief within two hours after dose, recurrence of headache within 24 hours, and the lack of use of rescue medications. Additional assessments included tolerability of each triptan. Using sumatriptan as the standard, 12.5-mg almotriptan has similar efficacy after two hours of treatment, with better tolerability and higher rates of pain-free intervals.

Further studies comparing almotriptan to the newer triptans are necessary; however, with the trials available, almotriptan does have potential benefits. Almotriptan, like the other second-generation triptans, has improved pharmacokinetic properties, potency, and selectivity for the 5-HT1B/1D receptor. Based on results from comparative trials, almotriptan causes fewer adverse events—a desirable profile in a migraine medication. Although almotriptan is less likely to provide complete relief with two hours, it has been shown to relieve associated symptoms of migraines (i.e., nausea, vomiting, photophobia), allowing patients to return to their daily activities. Clinical responses to almotriptan and the others in its class do vary among migraineurs and so clinicians should be aware of this when choosing an appropriate treatment for a particular patient. Although pricing data shows almotriptan to be the least expensive in its class, pharmacoeconomic studies are needed to determine which 5-HT1B/1D agonist is the most cost-effective in the treatment of migraine (Table 1).

REFERENCES