Tosymra (Sumatriptan) Nasal Spray Approved for the Acute Treatment of Migraine, with or without Aura

By Loretta Fala, Medical Writer

It is estimated that 39 million individuals in the United States, approximately 12% of the population, were affected by migraine headache in 2018.1 Approximately 85% of patients with chronic migraine are women.1 Migraine is a neurologic condition characterized by throbbing pain that usually affects one side of the head (but can affect both sides), and is often accompanied by visual disturbances, nausea, vomiting, tingling or numbness in the extremities, and extreme sensitivity to sound, light, and smell.1,2 If untreated, a migraine attack typically lasts from 4 hours to 72 hours.2

More than 90% of individuals report an inability to work or handle routine activities during a migraine episode. Migraine accounts for approximately $36 billion in annual US healthcare and lost productivity costs. Despite its notable prevalence, frequency, and seriousness, migraine remains underdiagnosed and undertreated.1

The treatments for migraine include acute therapy during an attack and preventive therapy to reduce the severity or frequency of attacks. Acute treatments for migraine include analgesics; triptans; and ergots or ergot-derivatives. Other treatments may include antinausea medications, opioids (usually only for patients who are unable to take triptans or ergots), and glucocorticoids. Preventive therapy is generally used for patients who have ≥4 attacks monthly, attacks of long duration, or an inadequate response to medications. Preventive treatments include cardiovascular drugs, antidepressants, antiseizure drugs, the recently approved erenumab-aooe (Aimovig), and onabotulinumtoxinA (Botox).3

Tosymra a New Option for Adults with Migraine

On January 27, 2019, sumatriptan nasal spray (Tosymra; Promius Pharma/Dr. Reddy’s Laboratories) was approved by the US Food and Drug Administration (FDA) for the acute treatment of migraine with or without aura in adults.4 Sumatriptan nasal spray is a selective 5-hydroxytryptamine_receptor agonist. A subcutaneous injection form of sumatriptan (Imitrex) was approved by the FDA in 1992 for the treatment of migraine.5,6

Sumatriptan nasal spray should only be used if a clear diagnosis of migraine has been determined. If the patient does not achieve a response after the first treatment for migraine attack, the diagnosis should be reconsidered before sumatriptan nasal spray is used in subsequent migraine attacks. Sumatriptan nasal spray is not indicated for migraine prevention or for the treatment of cluster headache.5

Mechanism of Action

Sumatriptan is a selective 5-HT_receptor agonist.5 Sumatriptan binds with high affinity to 5-HT_receptors and exerts agonist effects on these receptors located on intracranial blood vessels and trigeminal sensory nerves, which results in constriction of the cranial vessel and inhibition of proinflammatory neuropeptide release.5

Dosing and Administration

Sumatriptan nasal spray is available as a single-dose that delivers 10 mg of sumatriptan.5 The recommended dose of sumatriptan nasal spray is 10 mg delivered as a single spray into 1 nostril. Within a 24-hour period, the maximum cumulative dose of sumatriptan that may be used is 30 mg, with doses separated by at least 1 hour. Sumatriptan nasal spray may be used at least 1 hour after a dose of another sumatriptan drug.5

Clinical Trials

The efficacy of sumatriptan nasal spray was based on its relative bioavailability compared with sumatriptan subcutaneous injection (4 mg) in healthy adults.5,7 In an open-label, randomized, 3-way crossover study, patients received sumatriptan 10 mg via a monodose nasal spray delivery system (N = 73), sumatriptan 10 mg via subcutaneous injection (N = 75), or sumatriptan 6 mg via subcutaneous injection (N = 75).

Sumatriptan nasal spray was administered with 0.2% DDM (1-O-n-Dodecyl-beta-D-Maltopyranoside), a permeation enhancer. The relative bioavailability of sumatriptan 10-mg nasal spray was approximately 88% (90% confidence interval [CI], 82%-94%) of that obtained with a 4-mg sumatriptan subcutaneous injection and 58% (90% CI, 55%-62%) of that obtained after
a 6-mg subcutaneous injection of sumatriptan.5,7

Sumatriptan nasal spray (10 mg plus permeation enhancer) was evaluated in a randomized, double-blind phase 2 study that included 107 patients with a history of episodic migraine.8 At 2 hours postdose, significantly more patients receiving sumatriptan nasal spray were free of migraine pain than those receiving placebo (43.8% vs 22.5%, respectively; P = .044); this was also the case for other symptoms, including nausea, photophobia, and phonophobia, at 2 hours postdose.8

The dose responses for multiple doses of sumatriptan injection compared with placebo were examined in a single migraine attack, parallel-group study (Study 1). At 2 hours postdose, 57% of patients receiving sumatriptan 4 mg and 70% of patients receiving sumatriptan 6 mg achieved migraine pain relief (Table 1).5

Sumatriptan 6-mg injection was evaluated in 2 randomized, placebo-controlled trials (Studies 2 and 3) of 1104 patients with moderate or severe migraine pain (Table 2).5 In the sumatriptan group, the onset of migraine relief occurred in less than 10 minutes, with 70% of patients achieving headache relief within 1-hour postdose. Moreover, approximately 82% of patients receiving sumatriptan achieved headache relief, and 65% were pain-free within 2 hours postdose.5

### Adverse Events

In pooled, placebo-controlled studies of patients with migraine who received a single 6-mg dose injection of sumatriptan or placebo, the most common (incidence ≥5%) adverse reactions associated with sumatriptan were atypical sensations (42%), tingling sensations (14%), dizziness or vertigo (12%), warm or hot sensation (11%), flushing (7%), burning sensation (7%), feeling of heaviness (7%), pressure sensation (7%), numbness (5%), feeling of tightness (5%), chest discomfort (5%), weakness (5%), and neck pain or stiffness (5%).5

In an open-label study that evaluated the tolerability of sumatriptan over 6 months of repeated use, 46% of patients reported application-site reactions, including burning sensations in the nose, dysgeusia, and throat irritation; approximately 0.5% of the reported cases were severe.5

In postmarketing reporting, hypotension, palpitations, dizziness, and tremor have been reported with sumatriptan nasal spray, tablets, and injection.5

### Contraindications

Sumatriptan is contraindicated in patients with ischemic coronary artery disease (CAD; angina pectoris, history of myocardial infarction, or documented silent ischemia) or coronary artery vasospasm, including Prinzmetal’s angina; Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders; a history of stroke, transient ischemic attack, or hemiplegic or basilar migraine; and peripheral vascular disease. Other contraindications include ischemic bowel disease; uncontrolled hypertension; or recent use (within 24 hours) of ergotamine-containing drugs, ergot-type drugs, or another 5-HT, agonist; concurrent administration of a monoamine oxidase inhibitor (MAOI)-A or recent use (within 2 weeks) of an MAOI-A; hypersensitivity to sumatriptan; and severe hepatic impairment.5

### Drug Interactions

Ergot-containing drugs can cause prolonged vasoconstrictive reactions; thus, ergotamine-containing or ergot-type drugs are contraindicated for use within 24 hours of sumatriptan use. Because MAOI-As increase the systemic

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**Table 1** Efficacy and Safety of Sumatriptan Injection, 4-mg and 6-mg Doses, in Patients with Migraine: Study 1

<table>
<thead>
<tr>
<th>Study treatment</th>
<th>Patients achieving migraine relief</th>
<th>Adverse events, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At 10 minutes, %</td>
<td>At 30 minutes, %</td>
</tr>
<tr>
<td>4-mg sumatriptan injection</td>
<td>13</td>
<td>37</td>
</tr>
<tr>
<td>6-mg sumatriptan injection</td>
<td>22</td>
<td>56</td>
</tr>
<tr>
<td>Placebo</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

**Table 2** Efficacy of Sumatriptan 6-mg Injection After 1 and 2 Hours in Patients with Migraine: Studies 2 and 3

<table>
<thead>
<tr>
<th>Migraine or symptom relief at 1 hour/2 hours</th>
<th>Placebo, % (N = 190)</th>
<th>Sumatriptan injection 6 mg, % (N = 384)</th>
<th>Placebo, % (N = 180)</th>
<th>Sumatriptan injection 6 mg, % (N = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with pain relief (grade 0-1), N, 1/2 hrs</td>
<td>18/31b</td>
<td>70/81c</td>
<td>26/39b</td>
<td>70/82c</td>
</tr>
<tr>
<td>Patients with no pain, N, 1/2 hrs</td>
<td>51/1b</td>
<td>48/55c</td>
<td>13/19b</td>
<td>49/55c</td>
</tr>
<tr>
<td>Patients without nausea, N, 1/2 hrs</td>
<td>48/56b</td>
<td>73/82c</td>
<td>50/33b</td>
<td>73/81c</td>
</tr>
<tr>
<td>Patients without phobia, N, 1/2 hrs</td>
<td>23/31b</td>
<td>56/72c</td>
<td>25/35b</td>
<td>58/71c</td>
</tr>
<tr>
<td>Patients with little or no clinical disability, N, 1/2 hrs</td>
<td>34/42c</td>
<td>76/85c</td>
<td>34/46c</td>
<td>76/84c</td>
</tr>
</tbody>
</table>

*Note: Although 6 sumatriptan doses were examined, only 2 are included here. The efficacy of sumatriptan nasal spray (10 mg) was demonstrated based on bioavailability compared with sumatriptan 4-mg subcutaneous injection.

Relief was defined as the reduction of moderate or severe pain to no or mild pain after dosing without the use of a rescue medication.

Source: Tosymra (sumatriptan) nasal spray prescribing information; January 2019.

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**Table 3** Efficacy of Sumatriptan 6-mg Injection After 1 and 2 Hours in Patients with Migraine: Studies 2 and 3
exposure of sumatriptan, their concurrent use is contraindicated. The use of other 5-HT\(^1\) agonists (eg, triptans) and sumatriptan within 24 hours of each other is contraindicated because of the potential for additive vasospastic effects. Serotonin syndrome can occur when the triptans are coadministered with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and MAOIs.\(^5\)

**Use in Specific Populations**

Data from a prospective pregnancy exposure registry and other epidemiologic studies of pregnant women exposed to sumatriptan did not show more birth defects than in the general population. However, in animal studies, oral sumatriptan was linked to embryolethality and fetal abnormalities, and subcutaneous sumatriptan was associated with embryolethality.\(^5\)

After subcutaneous administration, sumatriptan is excreted in human milk. The health benefits of breastfeeding and the mother’s clinical need for sumatriptan should be weighed against potential side effects on the breastfed child.\(^5\)

Dose selection for patients aged ≥65 years should start cautiously, at the low-end dosing range.\(^5\)

**Warnings and Precautions**

Although rare, reports of serious cardiac adverse reactions, including acute myocardial infarction, have occurred within several hours after sumatriptan administration, some occurring in patients without known CAD. The 5-HT\(^1\) agonists, including sumatriptan, have been associated with coronary artery vasospasm in patients with or without a history of CAD. Certain patients should be evaluated for cardiovascular risk factors before starting therapy.\(^5\)

Potentially fatal cardiac rhythm disturbances, including ventricular tachycardia and ventricular fibrillation leading to death, have been reported within a few hours after 5-HT\(^1\), agonist use. If any of these occur, sumatriptan should be promptly discontinued.\(^5\)

After treatment with sumatriptan injection, tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw have been frequently reported; these sensations are generally noncardiac in origin. Patients with a high cardiac risk should have a cardiac evaluation.\(^5\)

Cerebrovascular events, some fatal, have occurred in patients who have received 5-HT\(^1\), agonist treatment. Sumatriptan should be discontinued if a cerebrovascular event occurs.\(^5\)

Noncoronary vasospastic reactions, such as peripheral vascular, gastrointestinal vascular ischemia and infarction, splenic infarction, and Raynaud’s syndrome, can occur with sumatriptan use. Transient and permanent blindness and partial vision loss have been reported with the use of 5-HT\(^1\), agonists.\(^5\)

The overuse of acute migraine medications may exacerbate headache, leading to medication overuse headache, which may present as a migrainelike daily headache or as an increased frequency of migraine attacks.\(^3\)

Serotonin syndrome may occur, particularly when sumatriptan is coadministered with selective SSRIs, SNRIs, tricyclic antidepressants, and MAOIs. If serotonin syndrome is suspected, sumatriptan should be discontinued.\(^5\)

Although rare, significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has occurred in patients receiving 5-HT\(^1\), agonists, including patients without a history of hypertension. Blood pressure should be monitored in patients receiving sumatriptan.\(^5\)

Hypersensitivity reactions, including angioedema and anaphylaxis that can be life-threatening or fatal, have occurred in patients who received treatment with sumatriptan.\(^5\)

After sumatriptan administration, seizures have occurred. Sumatriptan treatment should be used with caution in patients who have a history of epilepsy or a condition with an increased risk for seizures.\(^5\)

**Conclusion**

The approval of sumatriptan nasal spray provides patients with a new, fast-acting option for the acute treatment of migraine, with or without aura. Sumatriptan nasal spray was shown to have a relative bioavailability comparable with sumatriptan 4-mg subcutaneous injection. At 2 hours postdose, a significantly greater proportion of patients receiving sumatriptan nasal spray achieved freedom from migraine pain compared with placebo.

**References**