Use only if a clear diagnosis of migraine has been established. If a patient has had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation (peripheral vascular disease), do not use TOSYMRA. TOSYMRA is not indicated for the treatment of cluster headache.

Increased blood pressure including a sudden severe increase may occur in some patients treated with TOSYMRA. TOSYMRA is contraindicated in patients with a history of heart disease if you:

- have heart disease
- have high blood pressure
- have had a heart attack
- have had a stroke
- have a history of high blood pressure
- have a heart condition that can be caused by increased blood pressure

Inform your healthcare provider if you have any of the following symptoms of a heart attack:

- chest pain or discomfort
- shortness of breath
- cold sweat
- nausea or vomiting
- lightheadedness
- fast or uneven heartbeat
- pain or discomfort in one or both arms, the back, neck, jaw, or stomach

Inform your healthcare provider if you have any of the following symptoms of a stroke or transient ischemic attack (TIA):

- weakness or numbness in the face, arm, or leg
- difficulty speaking
- trouble seeing in one or both eyes
- trouble walking
- dizziness
- confusion

Inform your healthcare provider if you have any of the following symptoms of high blood pressure:

- headache
- blurred vision
- nosebleeds
- increased thirst
- increased body weight

Hypersensitivity reactions, including angioedema and anaphylaxis, have occurred in patients treated with TOSYMRA. TOSYMRA should be used with caution in patients who have a history of asthma, chronic obstructive pulmonary disease (COPD), or other respiratory diseases.

Other Vasospasm Reactions

Inhibitor (4)

Monoamine Oxidase‑A (MAO)‑A inhibitors increase systemic exposure by 2‑fold. Therefore, the use of TOSYMRA is contraindicated with MAO‑A inhibitors. Take TOSYMRA 24 hours after stopping an MAO‑A inhibitor. The use of TOSYMRA is contraindicated in patients shown to have CAD and should be used with caution in patients with CAD.

Inhibitors and Serotonin 1 Agonists

Combining a monoamine oxidase‑A (MAO)‑A inhibitor, including TOSYMRA, with other 5‑HT1 agonists (e.g., triptans) within 24 hours of each other is contraindicated. Taking TOSYMRA within 24 hours of a 5‑HT1 agonist, rule out a vasospastic reaction before receiving additional medication.

Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina

Cardiac risk. The use of TOSYMRA is contraindicated in patients shown to have CAD and should be used with caution in patients with CAD.

Periodic cardiovascular evaluation in intermittent long‑term users of TOSYMRA.

The maximum cumulative dose that may be given in a 24‑hour period is 30 mg, with an initial dose of 10 mg.

POSTMARKETING EXPERIENCE

Dizziness/vertigo

Myalgia

Throat discomfort

Foot tingling

Muscle cramps

Nausea or vomiting

Increased heart rate

Diaphoresis

Palpitations

Anxiety

Headache

Increased blood pressure

Distress

Experienced

TOSYMRA is not used to prevent or decrease the number of migraines you have.

If your headaches get worse, your healthcare provider may decide to stop your treatment with TOSYMRA. If your headaches get worse and do not go away, talk to your healthcare provider about how to best manage your headaches.

Know the medicines you take. Keep a list of them to show your healthcare provider. TOSYMRA is not used to prevent or decrease the number of migraines you have. If your headaches get worse, your healthcare provider may decide to stop your treatment with TOSYMRA. If your headaches get worse and do not go away, talk to your healthcare provider about how to best manage your headaches.
PATIENT COUNSELING INFORMATION

How to Use TOSYMRA

It is unknown what effect hemodialysis or peritoneal dialysis has on the serum clearance or bioavailability of TOSYMRA. Therefore, if patients with severe renal impairment are dosed with TOSYMRA, specific monitoring and dose adjustments may be necessary. However, patients with moderate to mild renal impairment (GFR 30–80 mL/min) can be dosed as usual.

Advise patients to notify their healthcare provider if they become pregnant during treatment with TOSYMRA. There is no information available regarding the effects of TOSYMRA on the growing fetus. However, as a precaution, tell patients to avoid pregnancy during treatment with TOSYMRA.

Treatment of Severe Migraine

The efficacy of TOSYMRA is based on the relative bioavailability of TOSYMRA nasal spray as compared to TOSYMRA subcutaneous injection. The relative bioavailability of TOSYMRA was approximately 87% in a single ascending dose study in which 73 healthy subjects were treated with 10 mg of TOSYMRA nasal spray. While the bioavailability of TOSYMRA in healthy volunteers has been evaluated, no additional direct bioavailability data are available for patients with migraine.

The most common side effects of TOSYMRA include:

- Nausea
- Dizziness
- Feeling of tightness
- Headache
- Throat irritation
- Numbness
- Tingling

If these symptoms become severe or last for more than 30 minutes, patients should seek medical advice immediately.

Keep TOSYMRA and all medicines out of the reach of children. Store between 68° to 77°F (20° to 25°C).

What are the ingredients in TOSYMRA?

TOSYMRA contains the following active substance:

- Sumatriptan (50 mg)

It also contains the following inactive ingredients:

- Maltoside
- Potassium phosphate dibasic anhydrous in water for injection.

What should I do if I think I have an overdose of TOSYMRA?

If you think you may have an overdose of TOSYMRA, especially if you are experiencing severe side effects, seek medical advice immediately. Overdoses would be expected from animal data. The relationship was found to be as shown in Table 2.

Table 2: Relationship between dosage and mortality in animals treated with sumatriptan injection (mg/kg/day) for 14 days

<table>
<thead>
<tr>
<th>Dosage (mg/kg/day)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>0.0</td>
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<td>5</td>
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<td>60</td>
<td>0.0</td>
</tr>
<tr>
<td>80</td>
<td>0.0</td>
</tr>
</tbody>
</table>

It is unknown what effect hemodialysis or peritoneal dialysis has on the serum clearance or bioavailability of TOSYMRA. Therefore, if patients with severe renal impairment are dosed with TOSYMRA, specific monitoring and dose adjustments may be necessary. However, patients with moderate to mild renal impairment (GFR 30–80 mL/min) can be dosed as usual.

It is important to note that TOSYMRA is currently not approved for use in children under the age of 18 years. Safety and effectiveness of TOSYMRA in pediatric patients have not been established. Therefore, should be used with caution in children.

In Study 1, 6 different doses of sumatriptan injection (n = 30 each group) were compared for their effectiveness in treating migraine. Lower doses of sumatriptan injection may also prove effective, although the proportion of patients obtaining adequate relief was decreased and the latency to that effect increased.

The efficacy of TOSYMRA is based on the relative bioavailability of TOSYMRA nasal spray as compared to TOSYMRA subcutaneous injection. The relative bioavailability of TOSYMRA was approximately 87% in a single ascending dose study in which 73 healthy subjects were treated with 10 mg of TOSYMRA nasal spray. While the bioavailability of TOSYMRA in healthy volunteers has been evaluated, no additional direct bioavailability data are available for patients with migraine.

In Study 2, the onset of pain relief following a subcutaneous injection of sumatriptan was compared across different treatment groups. The onset of pain relief was observed in 80% of patients within 10 minutes, 88% within 30 minutes, and 94% within 60 minutes. The onset of pain relief in Study 3 was similar to that in healthy male subjects (mean age: 30 years).

The mechanism of action of TOSYMRA involves the serotoninergic system, with specific binding to 5-HT1B, 5-HT1D, and 5-HT1F receptors. This binding is responsible for the vasoconstriction of the va
deral arteries, which helps to relieve pain.

Peripheral (Small) Arteries

Peripheral vascular resistance is increased following the administration of TOSYMRA, resulting in relief of headache.

Absorption

Following nasal administration of 10 mg TOSYMRA in 73 healthy subjects, the relative bioavailability of TOSYMRA was approximately 87% [90% confidence interval (CI) 64–99%]. The absolute bioavailability of TOSYMRA in healthy volunteers (N = 18) was determined by dividing the area under the serum concentration-time curve (AUC) following the administration of 6 mg of subcutaneous TOSYMRA into the deltoid area of the arm in 9 males and females (mean age: 28 years). The AUC following subcutaneous administration was 5.6 times higher than that following nasal administration. The peak serum concentration (Cmax) was observed at 16 ± 12 minutes following subcutaneous administration, and at 7 ± 5 minutes following nasal administration. The relative bioavailability of TOSYMRA was determined to be 87% [90% CI 70–105%].

Age

The efficacy and safety of TOSYMRA have been evaluated in several studies involving patients aged 18 to 65 years. The efficacy of TOSYMRA was similar in patients aged ≥65 years compared to those aged 18–65 years.

Following subcutaneous administration of 50 mg of TOSYMRA in 73 healthy volunteers (mean age: 30 years), the mean (+ standard deviation) Cmax was 279 ± 132 ng/mL, and the time to Cmax was 19 ± 9 minutes. Following nasal administration of 10 mg TOSYMRA in 92 healthy volunteers (mean age: 30 years), the mean Cmax was 31 ± 13 ng/mL, and the time to Cmax was 7 ± 5 minutes.

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As with any medication, some patients may experience side effects. Common side effects of TOSYMRA include:

- Nausea
- Dizziness
- Feeling of tightness
- Headache
- Throat irritation
- Numbness
- Tingling

If these symptoms become severe or last for more than 30 minutes, patients should seek medical advice immediately.

Keep TOSYMRA and all medicines out of the reach of children. Store between 68° to 77°F (20° to 25°C). Do not test before use.