

The most common side effects of TOSYMRA include:

• tingling

• burning feeling

• flushing

• application site (nasal) reactions

• dizziness

• feeling of heaviness

• feeling of tightness

• abnormal taste

• feeling warm or hot

• feeling of pressure

• numbness

• throat irritation

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of TOSYMRA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TOSYMRA?

• Store between 68° to 77°F (20° to 25°C)

• Do not store in the refrigerator or freeze.

• Do not test before use.

Keep TOSYMRA and all medicines out of the reach of children.

General information about the safe and effective use of TOSYMRA.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use TOSYMRA for a condition for which it was not prescribed. Do not give TOSYMRA to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about TOSYMRA that is written for healthcare professionals.

For more information, go to www.upsher-smith.com or call 1-888-650-3789.

What are the ingredients in TOSYMRA?

Active ingredient: sumatriptan

Inactive ingredients: citric acid monohydrate, n-Dodecyl beta-D-maltoside, potassium phosphate monobasic, sodium chloride, and sodium phosphate dibasic anhydrous in water for injection.

Manufactured for

UPSHER-SMITH LABORATORIES, LLC

Maple Grove, MN 55369

TOSYMRA is a registered trademark of Upsher-Smith Laboratories, LLC.

This product may be covered by one or more U.S. patent(s). See www.uslpatents.com.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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8.2 Lactation

Risk Summary

Sumatriptan is excreted in human milk following subcutaneous administration (*see Data*). There are no data on the effects of sumatriptan on the breastfed infant or the effects of sumatriptan on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TOSYMRA and any potential adverse effects on the breastfed infant from sumatriptan or from the underlying maternal condition.

Clinical Considerations

Infant exposure to sumatriptan can be minimized by avoiding breastfeeding for 12 hours after treatment with TOSYMRA.

Data

Following subcutaneous administration of a 6 mg dose of sumatriptan injection in 5 lactating volunteers, sumatriptan was present in milk.

8.4 Pediatric Use

Safety and effectiveness of TOSYMRA in pediatric patients have not been established. TOSYMRA is not recommended for use in patients younger than 18 years of age.

Two controlled clinical trials evaluated sumatriptan nasal spray (5 mg to 20 mg) in 1,248 pediatric migraineurs 12 to 17 years of age who treated a single attack. The trials did not establish the efficacy of sumatriptan nasal spray compared with placebo in the treatment of migraine in pediatric patients. Adverse reactions observed in these clinical trials were similar in nature to those reported in clinical trials in adults.

Five controlled clinical trials (2 single-attack trials, 3 multiple-attack trials) evaluating oral sumatriptan (25 mg to 100 mg) in pediatric subjects 12 to 17 years of age enrolled a total of 701 pediatric migraineurs. These trials did not establish the efficacy of oral sumatriptan compared with placebo in the treatment of migraine in pediatric patients. Adverse reactions observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse reactions in these patients appeared to be both dose- and age-dependent, with younger patients reporting reactions more commonly than older pediatric patients.

Post-marketing experience documents that serious adverse reactions have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal sumatriptan. These reports include reactions similar in nature to those reported rarely in adults, including stroke, visual loss, and death. A myocardial infarction has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Clinical data to determine the frequency of serious adverse reactions in pediatric patients who might receive subcutaneous, oral, or intranasal sumatriptan are not presently available.

8.5 Geriatric Use

Clinical trials of sumatriptan did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. 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.

A cardiovascular evaluation is recommended for geriatric patients who have other cardiovascular risk factors (e.g., diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving TOSYMRA [*see Warnings and Precautions (5.1)*].

10 OVERDOSAGE

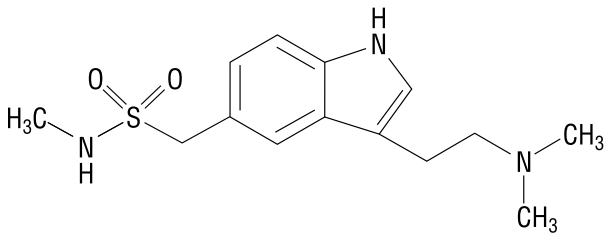
Coronary vasospasm was observed after intravenous administration of sumatriptan injection [*see Contraindications (4)*]. Overdoses would be expected from animal data (dogs at 0.1 g/kg, rats at 2 g/kg) to possibly cause convulsions, tremor, inactivity, erythema of the extremities, reduced respiratory rate, cyanosis, ataxia, mydriasis, injection site reactions (desquamation, hair loss, and scab formation), and paralysis.

The elimination half-life of sumatriptan is about 2 hours [*see Clinical Pharmacology (12.3)*], and therefore monitoring of patients after overdose with TOSYMRA should continue for at least 10 hours or while symptoms or signs persist.

It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.

11 DESCRIPTION

TOSYMRA contains sumatriptan, a selective 5-HT_{1B/1D} receptor agonist. Sumatriptan is chemically designated as 1-[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]-N-methylmethanesulfonamide, and it has the following structure:



The empirical formula is C₁₄H₂₁N₃O₃S, representing a molecular weight of 295.40. Sumatriptan is a white to pale yellow powder that is very slightly soluble in water.

TOSYMRA nasal spray is a clear, pale yellow to yellow colored liquid. Each 100 µL of TOSYMRA contains 10 mg of sumatriptan in single-dose aqueous buffered solution containing citric acid monohydrate, n-Dodecyl beta-D-maltoside, potassium phosphate monobasic, sodium chloride, and sodium phosphate dibasic anhydrous in water for injection.

The pH range of solution is approximately 5.0 to 6.0 and the osmolality is between 270 to 330 mOsmol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sumatriptan binds with high affinity to human cloned 5-HT_{1B/1D} receptors. Sumatriptan presumably exerts its therapeutic effects in the treatment of migraine headache through agonist effects at the 5-HT_{1B/1D} receptors on intracranial blood vessels and sensory nerves of the trigeminal system, which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

12.2 Pharmacodynamics

Blood Pressure

Significant elevation in blood pressure, including hypertensive crisis, has been reported in patients with and without a history of hypertension [*see Warnings and Precautions (5.8)*].

Peripheral (Small) Arteries

In healthy volunteers (N = 18), a trial evaluating the effects of sumatriptan on peripheral (small vessel) arterial reactivity failed to detect a clinically significant increase in peripheral resistance.

Heart Rate

Transient increases in blood pressure observed in some subjects in clinical trials carried out during sumatriptan's development as a treatment for migraine were not accompanied by any clinically significant changes in heart rate.

12.3 Pharmacokinetics

Following nasal administration of 10 mg TOSYMRA in 73 healthy subjects, the relative bioavailability of TOSYMRA was approximately 87% [90% confidence interval (CI) 82 to 94] of that obtained following 4 mg subcutaneous injection of sumatriptan. The relative bioavailability of TOSYMRA was 58% [90% CI 55 to 62] following 6 mg subcutaneous injection of sumatriptan.

Absorption

Peak plasma concentration of sumatriptan was observed in a median time of 10 minutes (range 5 to 23 minutes). After single nasal administration of the 10 mg dose, the mean (CV%) C_{max} and AUC were 51.8 ng/mL (58%) and 60.70 ng•hr/mL (42%), respectively.

Distribution

Sumatriptan protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL, is low; approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated.

Following a 6-mg subcutaneous injection into the deltoid area of the arm in 9 males (mean age: 33 years, mean weight: 77 kg) the volume of distribution central compartment of sumatriptan was 50 ± 8 liters and the distribution half-life was 15 ± 2 minutes.

Elimination

The elimination half-life of sumatriptan following administration of TOSYMRA is 2.44 ± 1.00 hours.

Metabolism

In vitro studies with human microsomes suggest that sumatriptan is metabolized by MAO, predominantly the A isoenzyme. Most of a radiolabeled dose of sumatriptan excreted in the urine is the major metabolite indole acetic acid (IAA) or the IAA glucuronide, both of which are inactive.

Excretion

After a single 6 mg subcutaneous dose, 22% ± 4% was excreted in the urine as unchanged sumatriptan and 38% ± 7% as the IAA metabolite.

Following a 6 mg subcutaneous injection into the deltoid area of the arm, the systemic clearance of sumatriptan was 1,194 ± 149 mL/min and the terminal half-life was 115 ± 19 minutes.

Specific Populations

Age

The pharmacokinetics of sumatriptan in the elderly (mean age: 72 years, 2 males and 4 females) and in subjects with migraine (mean age: 38 years, 25 males and 155 females) were similar to that in healthy male subjects (mean age: 30 years).

Patients with Hepatic Impairment

The effect of hepatic disease on the pharmacokinetics of TOSYMRA has not been evaluated. The effect of mild to moderate hepatic disease on the pharmacokinetics of subcutaneously administered sumatriptan has been evaluated. There were no significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in moderately hepatically impaired subjects compared with healthy controls. The pharmacokinetics of subcutaneously administered sumatriptan in patients with severe hepatic impairment has not been studied. The use of TOSYMRA in this population is contraindicated [*see Contraindications (4)*].

Racial Groups

The systemic clearance and C_{max} of subcutaneous sumatriptan were similar in black (n=34) and Caucasian (n=38) healthy male subjects. TOSYMRA has not been evaluated for race differences.

Drug Interaction Studies

Monamine Oxidase-A Inhibitors

In a trial of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of subcutaneous sumatriptan, resulting in a 2-fold increase in the area under the sumatriptan plasma concentration-time curve (AUC), corresponding to a 40% increase in elimination half-life.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In carcinogenicity studies in mouse and rat, sumatriptan was administered orally for 78 weeks and 104 weeks, respectively, at doses up to 160 mg/kg/day (the highest dose in rat was reduced from 360 mg/kg/day during Week 21). There was no evidence in either species of an increase in tumors related to sumatriptan administration.

Mutagenesis

Sumatriptan was negative in *in vitro* (bacterial reverse mutation [Ames], gene cell mutation in Chinese hamster V79/HGPRT, chromosomal aberration in human lymphocytes) and *in vivo* (rat micronucleus) assays.

Impairment of Fertility

When sumatriptan (0, 5, 50, 500 mg/kg/day) was administered orally to male and female rats prior to and throughout the mating period, there was a treatment-related decrease in fertility secondary to a decrease in mating in animals treated with doses greater than 5 mg/kg/day. It is not clear whether this finding was due to an effect on males or females or both.

When sumatriptan was administered by subcutaneous injection to male and female rats prior to and throughout the mating period, there was no evidence of impaired fertility at doses up to 60 mg/kg/day.

13.2 Animal Toxicology and/or Pharmacology

Corneal Opacities

Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dose tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established.

14 CLINICAL STUDIES

The efficacy of TOSYMRA is based on the relative bioavailability of TOSYMRA nasal spray compared to sumatriptan subcutaneous injection (4 mg) in healthy adults [*see Clinical Pharmacology (12.3)*].

In controlled clinical trials enrolling more than 1,000 patients during migraine attacks who were experiencing moderate or severe pain and 1 or more of the symptoms enumerated in Table 3, onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Lower doses of sumatriptan injection may also prove effective, although the proportion of patients obtaining adequate relief was decreased and the latency to that relief is greater with lower doses.

In Study 1, 6 different doses of sumatriptan injection (n = 30 each group) were compared with placebo (n = 62) in a single-attack, parallel-group design; the dose-response relationship was found to be as shown in Table 2.

Table 2: Proportion of Patients with Migraine Relief and Incidence of Adverse Reactions by Time and by Sumatriptan Dose in Study 1

Dose of sumatriptan Injection	Percent Patients with Relief ^a				Adverse Reactions Incidence (%)
	at 10 Minutes	at 30 Minutes	at 1 Hour	at 2 Hours	
Placebo	5	15	24	21	55
1 mg	10	40	43	40	63
2 mg	7	23	57	43	63
3 mg	17	47	57	60	77
4 mg ^b	13	37	50	57	80
6 mg	10	63	73	70	83
8 mg	23	57	80	83	93

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

^b Efficacy of Tosymra nasal spray was demonstrated based on bioavailability to 4 mg sumatriptan SC injection.

In 2 randomized, placebo-controlled clinical trials of sumatriptan injection 6 mg in 1,104 patients with moderate or severe migraine pain (Studies 2 and 3), the onset of relief was less than 10 minutes. Headache relief, as defined by a reduction in pain from severe or moderately severe to mild or no headache, was achieved in 70% of the patients within 1 hour of a single 6 mg subcutaneous dose of sumatriptan injection. Approximately 82% and 65% of patients treated with sumatriptan 6 mg had headache relief and were pain free within 2 hours, respectively.

Table 3 shows the 1- and 2-hour efficacy results for sumatriptan injection 6 mg in Studies 2 and 3.

Table 3: Proportion of Patients with Pain Relief and Relief of Migraine Symptoms after 1 and 2 Hours of Treatment in Studies 2 and 3

	Study 2		Study 3	
	Placebo (n = 190)	Sumatriptan Injection 6 mg (n = 384)	Placebo (n = 180)	Sumatriptan Injection 6 mg (n = 350)
1-Hour Data				
Patients with pain relief (Grade 0/1)	18%	70% ^a	26%	70% ^a
Patients with no pain	5%	48% ^a	13%	49% ^a
Patients without nausea	48%	73% ^a	50%	73% ^a
Patients without photophobia	23%	56% ^a	25%	58% ^a
Patients with little or no clinical disability ^b	34%	76% ^a	34%	76% ^a

	Study 2		Study 3	
	Placebo ^c	Sumatriptan Injection 6 mg ^d	Placebo ^c	Sumatriptan Injection 6 mg ^d
2-Hour Data				
Patients with pain relief (Grade 0/1)	31%	81% ^a	39%	82% ^a
Patients with no pain	11%	63% ^a	19%	65% ^a
Patients without nausea	56%	82% ^a	63%	81% ^a
Patients without photophobia	31%	72% ^a	35%	71% ^a
Patients with little or no clinical disability ^b	42%	85% ^a	49%	84% ^a

^a P<0.05 versus placebo.

^b A successful outcome in terms of clinical disability was defined prospectively as ability to work mildly impaired or ability to work and function normally.

^c Includes patients that may have received an additional placebo injection 1 hour after the initial injection.

^d Includes patients that may have received an additional 6 mg of sumatriptan injection 1 hour after the initial injection.

Sumatriptan injection also relieved photophobia, phonophobia (sound sensitivity), nausea, and vomiting associated with migraine attacks.

The efficacy of sumatriptan injection was unaffected by whether or not the migraine was associated with aura, duration of attack, gender or age of the patient, or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

• TOSYMRA® 10 mg (NDC 0245-0812-89) contains sumatriptan and is supplied as a ready-to-use, single-dose, disposable unit.

• Each carton contains 6 units (NDC 0245-0812-61) and a Patient Information and Instructions for Use leaflet.

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F).

Do not store in the refrigerator or freezer. Do not test before use.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Risk of Myocardial Ischemia and/or Infarction, Prinzmetal's Angina, Other Vasospasm-Related Events, Arrhythmias, and Cerebrovascular Events

Inform patients that TOSYMRA may cause serious cardiovascular side effects such as myocardial infarction or stroke. Although serious cardiovascular events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, irregular heartbeat, significant rise in blood pressure, weakness, and slurring of speech and should ask for medical advice when observing any indicative sign or symptoms are observed. Apprise patients of the importance of this follow-up [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.5, 5.8)*].

Hypersensitivity Reactions

Inform patients that anaphylactic reactions have occurred in patients receiving sumatriptan. Such reactions can be life threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens [*see Contraindications (4)* and *Warnings and Precautions (5.9)*].

Concomitant Use with Other Triptans or Ergot Medications

Inform patients that use of TOSYMRA within 24 hours of another triptan or an ergot-type medication (including dihydroergotamine or methysergide) is contraindicated [*see Contraindications (4), Drug Interactions (7.1, 7.3)*].

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with the use of TOSYMRA or other triptans, particularly during combined use with SSRIs, SNRIs, TCAs, and MAO inhibitors [*see Warnings and Precautions (5.7), Drug Interactions (7.4)*].

Medication Overuse Headache

Inform patients that use of acute migraine drugs for 10 or more days per month may lead to an exacerbation of headache and encourage patients to record headache frequency and drug use (e.g., by keeping a headache diary) [*see Warnings and Precautions (5.6)*].

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant during treatment or plan to become pregnant [*see Use in Specific Populations (8.1)*].

Lactation

Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed [*see Use in Specific Populations (8.2)*].

Ability to Perform Complex Tasks

Treatment with TOSYMRA may cause somnolence and dizziness; instruct patients to evaluate their ability to perform complex tasks during migraine attacks and after administration of TOSYMRA.

Local Irritation

Inform patients that they may experience local irritation of their nose, mouth, and throat; and changes in taste [*see Warnings and Precautions (5.11)*].

How to Use TOSYMRA

Provide patients instruction on the proper use of TOSYMRA. Caution patients to avoid spraying the contents of the device in their eyes.

Manufactured for

UPSHER-SMITH LABORATORIES, LLC

Maple Grove, MN 55369

TOSYMRA is a registered trademark of Upsher-Smith Laboratories, LLC.

This product may be covered by one or more U.S. patent(s). See www.uslpatents.com.

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