Zembrace® SYMTOUCH® (sumatriptan injection) 3 mg

tosymra® (sumatriptan nasal spray) 10 mg

Prior Authorizations & Appeals Kit

Easy-to-follow instructions, templates, and checklists to help obtain insurance coverage

The information herein is provided for educational purposes only. Tonix Medicines cannot guarantee insurance coverage or reimbursement. Coverage and reimbursement may vary significantly by payer, plan and patient. It is the sole responsibility of the healthcare provider to select the proper codes and ensure the accuracy of all statements used in seeking coverage and reimbursement for an individual patient.

INDICATION:

Zembrace® SymTouch® and Tosymra® are indicated for the acute treatment of migraine with or without aura in adults.

CONTRAINDICATIONS:

Ischemic coronary artery disease or vasospasm (including Prinzmetal's angina); Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders; history of stroke or transient ischemic attack or hemiplegic or basilar migraine. These are not all of the contraindications for Zembrace® SymTouch® and Tosymra®.

Please see **Important Safety Information and Limitations of Use** on page 7 and accompanying full Prescribing Information for Zembrace® SymTouch® and Tosymra®
You may also visit **Zembrace-hcp.com** or **Tosymra-hcp.com**

How to Use This Kit

- We know you are busy. When filling out Prior Authorization (PA) paperwork, administrative error or missing required documents adds work for your staff.
- Use this kit as a guide to help ensure the insurance company has exactly what is needed to approve Zembrace® SymTouch® or Tosymra® coverage for your patients.

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Starting and Completing a Prior Authorization (PA)

Once a patient is prescribed Zembrace® SymTouch® or Tosymra®, their insurance plan may require a PA.

Generally, when it comes to Zembrace® SymTouch® or Tosymra®, PA criteria are fairly straightforward. Plans want to know which other medications have been tried without success or are contraindicated.

Following the checklist below will help minimize the need for appeals and denials.

PRIOR AUTHORIZATION (PA) CHECKLIST

Use the checklist below to help ensure you have proactively included information that may answer any questions and avoid denials due to administrative mistakes.

- ☐ Member Information: name, policy number, and date of birth
- ☐ Most current information for your patient's coverage plan
- ☐ Provider information
- ☐ Requested medication name, dose, and directions
- ☐ ICD-10 diagnosis codes for patient's condition
- ☐ List medications that have been tried and failed (if there is no section for this, add it to the notes section or as an attachment)
- ☐ Include clinical rationale for prescribing — see examples found in the template letter

ACUTE MIGRAINE MEDICATION EXAMPLES

Triptans	Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan (oral, nasal, or injectable), Zolmitriptan (oral or nasal)
Ergot Alkaloids	Dihydroergotamine
Ditan	Lasmiditan
CGRP modulator	Rimegepant, Ubrogepant

Did You Know?

The most common causes for a denial for a PA are:

- Omitting the patient's date of birth
- Outdated or incomplete insurance information
- Missing prescriber signature

Please see **Important Safety Information and Limitations of Use** on page 7 and accompanying full Prescribing Information for Zembrace® SymTouch® and Tosymra®
You may also visit **Zembrace-hcp.com** or **Tosymra-hcp.com**

Appealing a Prior Authorization (PA) Denial

WHAT HAPPENS WHEN A PA IS SUBMITTED AND DENIED?

Insurance companies must explain why a PA is denied and let your office know how to complete an appeal.

To complete an appeal, you will provide an appeal communication via a form or a letter. It's critical to include clinical language to support the treatment of the patient.

This letter comes from the prescriber. It should be submitted with a copy of the patient's relevant medical records. **Click the icon below to open an editable Word template of the letter.**

Zembrace® SymTouch® Prescriber Letter of Appeal Template

Tosymra® Prescriber Letter of Appeal Template

LETTER OF APPEAL CHECKLIST

- ☐ Include the patient's name, policy number, date of birth, PA denial reference number, and date of denial
- ☐ Acknowledge that you are familiar with the company's policy and state the reason for denial
- ☐ Patient history, diagnosis, current condition, and symptoms
- ☐ Include copies of relevant medical records (payers may want to see if any allergies or comorbidities are present)
- ☐ List of previous therapies tried and failed
- ☐ Duration of each therapy and why it was discontinued
- ☐ Why formulary-preferred agents are not options (if they have not already been listed as previous therapies) — see examples in the template letter
- ☐ Provide clinical support for your recommendation: this can include clinical trial data from the package insert
- ☐ If required, attach a Letter of Medical Necessity

Writing a Letter of Medical Necessity

In this letter, the prescriber outlines his/her clinical judgment about the diagnosis and proposed therapy, which can be submitted with prior authorization to prevent a denial.

Click the icons below to open an editable Word template of each letter.

Zembrace® SymTouch® Prescriber Letter of Medical Necessity Template

Tosymra® Prescriber Letter of Medical Necessity Template

MEDICAL NECESSITY LETTER CHECKLIST

- ☐ Date of birth, policy number, and denial reference number, if needed
- ☐ History, symptoms, and diagnosis
- ☐ What were the previous treatments? How long did each therapy last, and why was it discontinued?
- ☐ Provide specific reasons why step therapies or preferred formulary and not treatment options for the patient
- ☐ Summary of recommendations and phone number

ICD-10 codes for migraine[1]

TABLE 1

G43.009	Migraine without aura, not intractable, without status migrainosus	G43.809	Other migraine, not intractable, without status migrainosus
G43.019	Migraine without aura, intractable, without status migrainosus	G43.819	Other migraine, intractable, without status migrainosus
G43.109	Migraine with aura, not intractable, without status migrainosus	G43.909	Migraine, unspecified, not intractable, without status migrainosus
G43.119	Migraine with aura, intractable, without status migrainosus	G43.919	Migraine, unspecified, intractable, without status migrainosus

Disclaimer: These codes are presented for informational purposes only. They represent no statement, promise, or guarantee by Tonix Medicines concerning coverage and/or levels of reimbursement, payment, or charge and are not intended to increase or maximize reimbursement by any payer. It is the responsibility of the healthcare provider to determine the appropriate code(s) for service provided to his or her patient. Laws, regulations, and policies concerning reimbursement are complex and updated frequently. Although we have made an effort to be current as of January 2023, the information may not be current or comprehensive when you view it. Please consult the applicable payer organization with regard to local or actual coverage, reimbursement policies, and determination processes.

CONTRAINDICATIONS:

Peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; recent (i.e., within 24 hours) use of ergotamine-containing medication, ergot-type medication, or another 5-HT_1 agonist; concurrent or recent (within 2 weeks) use of a monoamine oxidase (MAO)-A inhibitor; known hypersensitivity to sumatriptan; severe hepatic impairment. These are not all of the contraindications for Zembrace® SymTouch® and Tosymra®.

IMPORTANT SAFETY INFORMATION

Zembrace® SymTouch® and Tosymra® are contraindicated inpatients with:

- Ischemic Coronary Artery Disease (CAD) or coronary artery vasospasm (including Prinzmetal's angina)
- Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders
- History of stroke or transient ischemic attack or history of hemiplegic or basilar migraine
- Peripheral vascular disease
- Ischemic bowel disease
- Uncontrolled hypertension
- Recent (i.e., within 24 hours) use of ergotamine-containing medication, ergot-type medication, or another 5-HT_1 agonist
- Concurrent or recent (within 2 weeks) use of a monoamine oxidase (MAO)-A inhibitor
- Known hypersensitivity to sumatriptan (angioedema and anaphylaxis seen)
- Severe hepatic impairment

There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of sumatriptan. Some of these reactions occurred in patients without known CAD. Zembrace SymTouch and Tosymra, like other 5-HT_1 agonists, may cause coronary artery vasospasm, even in patients without a history of CAD.

Perform a cardiovascular evaluation in triptan-naive patients who have multiple cardiovascular risk factors prior to receiving Zembrace SymTouch or Tosymra. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first dose of Zembrace SymTouch or Tosymra in a medically supervised setting and performing an ECG immediately following administration. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of Zembrace SymTouch or Tosymra.

Life-threatening disturbances of cardiac rhythm, leading to death, have been reported within a few hours following the administration of 5-HT_1 agonists. Discontinue Zembrace SymTouch and/or Tosymra if any of these cardiovascular disturbances occur.

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. Discontinue Zembrace SymTouch and/or Tosymra if a cerebrovascular event occurs.

Sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw commonly occur after treatment with sumatriptan injection and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk.

Zembrace SymTouch and Tosymra may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction, splenic infarction, and Raynaud's syndrome.

Overuse of acute migraine drugs may lead to medication overuse headache. Detoxification of patients and treatment of withdrawal symptoms may be necessary.

Serotonin syndrome may occur with Zembrace SymTouch and Tosymra, particularly during co-administration with selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, and MAO inhibitors. Discontinue Zembrace SymTouch and/or Tosymra if serotonin syndrome is suspected.

Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients treated with 5-HT_1 agonists, including patients without a history of hypertension. Monitor blood pressure in patients treated with Zembrace SymTouch and/or Tosymra.

Seizures have been reported following administration of sumatriptan. Some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. Zembrace SymTouch and/or Tosymra should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

Most common adverse reactions (≥5% and > placebo) with sumatriptan injection were injection site reactions (Zembrace SymTouch only), tingling, dizziness/vertigo, warm/hot sensation, burning sensation, feeling of heaviness, pressure sensation, flushing, feeling of tightness, and numbness. Additional common adverse reactions with Tosymra include application site reactions, dysgeusia, and throat irritation.

This safety information is not comprehensive. Please refer to the:

- Zembrace SymTouch full Prescribing Information, Patient Information, and Instructions for Use.
- Tosymra full Prescribing Information, Patient Information, and Instructions for Use.

You can also visit www.tonixpharma.com or call 1-888-650-3789. You are encouraged to report suspected adverse reactions to Tonix Medicines, Inc. at 1-888-869-7633 or to the FDA by visiting www.fda.gov/medwatch or calling 1-800-FDA-1088.

INDICATION AND USAGE: Zembrace SymTouch and Tosymra are indicated for the acute treatment of migraine with or without aura in adults.

Limitations of Use:

- Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated, reconsider the diagnosis before administering to treat any subsequent attacks.
- Zembrace SymTouch and Tosymra are not indicated for the preventive treatment of migraine or for the treatment of cluster headache.

Reference: 1. https://www.cms.gov/medicare/icd-10/2021-icd-10-cm. Updated December 16, 2020. Accessed 2023.

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ZEMBRACE SYMTOUCH- sumatriptan succinate solution
Tonix Medicines, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEMBRACE® SymTouch® safely and effectively. See full prescribing information for ZEMBRACE® SymTouch®.

ZEMBRACE® SymTouch® (sumatriptan succinate) Injection, for subcutaneous use
Initial U.S. Approval: 1992

INDICATIONS AND USAGE

ZEMBRACE SymTouch is a serotonin (5-$HT_{1B/1D}$) receptor agonist (triptan) indicated for:
- Acute treatment of migraine with or without aura in adults. (1)

Limitations of Use:
- Use only if a clear diagnosis of migraine has been established. (1)
- Not indicated for the prophylactic therapy of migraine. (1)

DOSAGE AND ADMINISTRATION

- For subcutaneous use only. (2.1)
- Acute treatment of migraine: 3 mg Single dose. (2.1)
- Maximum dose in a 24-hour period: 12 mg. Separate doses by at least 1 hour. (2.1)

DOSAGE FORMS AND STRENGTHS

- Injection: 3 mg prefilled, ready-to-use, single-dose disposable auto-injector. (3)

CONTRAINDICATIONS

- History of coronary artery disease or coronary vasospasm (4)
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders (4)
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine (4)
- Peripheral vascular disease (4)
- Ischemic bowel disease (4)
- Uncontrolled hypertension (4)
- Recent (within 24 hours) use of another 5-HT_1 agonist (e.g., another triptan) or of an ergotamine-containing medication (4)
- Concurrent or recent (past 2 weeks) use of monoamine oxidase-A inhibitor (4)
- Hypersensitivity to sumatriptan (angioedema and anaphylaxis seen) (4)
- Severe hepatic impairment (4)

WARNINGS AND PRECAUTIONS

- Myocardial ischemia/infarction and Prinzmetal's angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors. (5.1)
- Arrhythmias: Discontinue ZEMBRACE SymTouch if occurs. (5.2)
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness: Generally, not associated with myocardial ischemia; evaluate for coronary artery disease in patients at high risk. (5.3)
- Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Discontinue ZEMBRACE SymTouch if occurs. (5.4)
- Gastrointestinal ischemia and reactions, peripheral vasospastic reactions: Discontinue ZEMBRACE SymTouch if occurs. (5.5)
- Medication overuse headache: Detoxification may be necessary. (5.6)
- Serotonin syndrome: Discontinue ZEMBRACE SymTouch if occurs. (5.7)
- Seizures: Use with caution in patients with epilepsy or a lowered seizure threshold. (5.10)

ADVERSE REACTIONS

Most common adverse reactions (≥5% and > placebo) were injection site reactions, tingling, dizziness/vertigo, warm/hot sensation, burning sensation, feeling of heaviness, pressure sensation, flushing, feeling of tightness, and numbness/paresthesia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Tonix Medicines, Inc. at 1-888-869-7633

(1-888-TNXPMED) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZEMBRACE SymTouch is indicated for the acute treatment of migraine with or without aura in adults.

Limitations of Use:

- Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated with ZEMBRACE SymTouch, reconsider the diagnosis before ZEMBRACE SymTouch is administered to treat any subsequent attacks.
- ZEMBRACE SymTouch injection is not indicated for the prevention of migraine attacks.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of ZEMBRACE SymTouch is 3 mg injected subcutaneously.

The maximum cumulative injected dose that may be given in 24 hours is 12 mg, with doses of ZEMBRACE SymTouch separated by at least 1 hour. ZEMBRACE SymTouch may also be given at least 1 hour following a dose of another sumatriptan product.

2.2 Administration Using ZEMBRACE SymTouch

ZEMBRACE SymTouch is available as a prefilled, ready-to-use, single dose, disposable auto-injector containing 3 mg sumatriptan. With ZEMBRACE SymTouch, the needle penetrates approximately ¼ inch (6 mm). The injection is intended to be given subcutaneously. Do not administer by any other route. Instruct patients on the proper use of ZEMBRACE SymTouch and direct them to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle.

3 DOSAGE FORMS AND STRENGTHS

Injection: 3 mg sumatriptan in 0.5 mL prefilled, ready-to-use, single dose, disposable auto-injector.

4 CONTRAINDICATIONS

ZEMBRACE SymTouch injection 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 *[see Warnings and Precautions (5.1)]*.
- Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders *[see Warnings and Precautions (5.2)]*.
- History of stroke or transient ischemic attack (TIA) or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke *[see Warnings and Precautions (5.4)]*.
- Peripheral vascular disease *[see Warnings and Precautions (5.5)]*.
- Ischemic bowel disease *[see Warnings and Precautions (5.5)]*.
- Uncontrolled hypertension *[see Warnings and Precautions (5.8)]*.
- Recent (i.e., within 24 hours) use of ergotamine-containing medication, ergot-type medication (such as dihydroergotamine or methysergide), or another 5-hydroxytryptamine1 (5-HT_1) agonist *[see Drug Interactions (7.1, 7.3)]*.
- Concurrent administration of an MAO-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.
- Known hypersensitivity to sumatriptan (angioedema and anaphylaxis seen) *[see Warnings and Precautions (5.9)]*.
- Severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina

The use of ZEMBRACE SymTouch injection is contraindicated in patients with ischemic or vasospastic CAD. There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of sumatriptan injection. Some of these reactions occurred in patients without known CAD. 5-HT_1 agonists, including ZEMBRACE SymTouch injection, may cause coronary artery vasospasm (Prinzmetal's angina), even in patients without a history of CAD.

Perform a cardiovascular evaluation in triptan-naive patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving ZEMBRACE SymTouch injection. If there is evidence of CAD or coronary artery vasospasm, ZEMBRACE SymTouch injection is contraindicated. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first dose of ZEMBRACE SymTouch injection in a medically supervised setting and performing an electrocardiogram (ECG) immediately following ZEMBRACE SymTouch injection. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of ZEMBRACE SymTouch injection.

5.2 Arrhythmias

Life-threatening disturbances of cardiac rhythm, including ventricular tachycardia and ventricular fibrillation leading to death, have been reported within a few hours following

the administration of 5-HT_1 agonists. Discontinue ZEMBRACE SymTouch injection if these disturbances occur. ZEMBRACE SymTouch injection is contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.

5.3 Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure

Sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw commonly occur after treatment with sumatriptan injection and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. The use of ZEMBRACE SymTouch injection is contraindicated in patients with CAD and those with Prinzmetal's variant angina.

5.4 Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT_1 agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. Also, patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). Discontinue ZEMBRACE SymTouch injection if a cerebrovascular event occurs.

Before treating headaches in patients not previously diagnosed with migraine or in patients who present with atypical symptoms, exclude other potentially serious neurological conditions. ZEMBRACE SymTouch injection is contraindicated in patients with a history of stroke or TIA.

5.5 Other Vasospasm Reactions

ZEMBRACE SymTouch injection may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with abdominal pain and bloody diarrhea), splenic infarction, and Raynaud's syndrome. In patients who experience symptoms or signs suggestive of non-coronary vasospasm reaction following the use of any 5-HT_1 agonist, rule out a vasospastic reaction before receiving additional ZEMBRACE SymTouch injections.

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT_1 agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT_1 agonists have not been clearly established.

5.6 Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, combination of these drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches, or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

5.7 Serotonin Syndrome

Serotonin syndrome may occur with ZEMBRACE SymTouch injection, particularly during co-administration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors *[see Drug Interactions (7.4)]*. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. Discontinue ZEMBRACE SymTouch injection if serotonin syndrome is suspected.

5.8 Increase in Blood Pressure

Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has been reported on rare occasions in patients treated with 5-HT_1 agonists, including patients without a history of hypertension. Monitor blood pressure in patients treated with ZEMBRACE SymTouch. ZEMBRACE SymTouch injection is contraindicated in patients with uncontrolled hypertension.

5.9 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema and anaphylaxis, 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. ZEMBRACE SymTouch injection is contraindicated in patients with a history of hypersensitivity reaction to sumatriptan.

5.10 Seizures

Seizures have been reported following administration of sumatriptan. Some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. There are also reports in patients where no such predisposing factors are apparent. ZEMBRACE SymTouch injection should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Myocardial ischemia, myocardial infarction, and Prinzmetal's angina *[see Warnings and Precautions (5.1)]*
- Arrhythmias *[see Warnings and Precautions (5.2)]*
- Chest, throat, neck, and/or jaw pain/tightness/pressure *[see Warnings and Precautions (5.3)]*
- Cerebrovascular events *[see Warnings and Precautions (5.4)]*
- Other vasospasm reactions *[see Warnings and Precautions (5.5)]*
- Medication overuse headache *[see Warnings and Precautions (5.6)]*
- Serotonin syndrome *[see Warnings and Precautions (5.7)]*
- Increase in blood pressure *[see Warnings and Precautions (5.8)]*

- Hypersensitivity reactions *[see Contraindications (4), Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Placebo-Controlled Trials with Sumatriptan Injection

Migraine Headache: Table 1 lists adverse reactions that occurred in 2 US placebo-controlled clinical trials in migraine subjects (Studies 2 and 3), following either a single 6-mg dose of sumatriptan injection or placebo. Only reactions that occurred at a frequency of 2% or more in groups treated with sumatriptan injection 6 mg and that occurred at a frequency greater than the placebo group are included in Table 1.

Table 1: Adverse Reactions in Pooled Placebo-Controlled Trials in Patients with Migraine (Studies 2 and 3)

Adverse Reaction	**Percent of Subjects Reporting**	
	Sumatriptan Injection 6 mg Subcutaneous (n = 547)	**Placebo (n = 370)**
Atypical sensations	42	9
Tingling	14	3
Warm/hot sensation	11	4
Burning sensation	7	<1
Feeling of heaviness	7	1
Pressure sensation	7	2
Feeling of tightness	5	<1
Numbness	5	2
Feeling strange	2	<1
Tight feeling in head	2	<1
Cardiovascular		
Flushing	7	2
Chest discomfort	5	1
Tightness in chest	3	<1
Pressure in chest	2	<1
Ear, nose, and throat		
Throat discomfort	3	<1
Discomfort: nasal cavity/sinuses	2	<1
Injection site reaction*	59	24
Miscellaneous		
Jaw discomfort	2	0
Musculoskeletal		
Weakness	5	<1
Neck pain/stiffness	5	<1

Myalgia	2	<1
Neurological		
Dizziness/vertigo	12	4
Drowsiness/sedation	3	2
Headache	2	<1
Skin		
Sweating	2	1

* Includes injection site pain, stinging/burning, swelling, erythema, bruising, bleeding.

The incidence of adverse reactions in controlled clinical trials was not affected by gender or age of the patients. There were insufficient data to assess the impact of race on the incidence of adverse reactions.

Adverse Reactions in a Study with ZEMBRACE SymTouch

The most common adverse reactions in a placebo-controlled trial with ZEMBRACE SymTouch were injection site reactions (including injection site bruising, erythema, hemorrhage, induration, irritation, pain, paresthesia, pruritis, swelling, and urticaria), occurring in 30% of ZEMBRACE SymTouch-treated patients compared to 13% of placebo-treated patients. Adverse reactions with ZEMRACE SymTouch are expected to be similar to those observed with sumatriptan injection.

6.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of sumatriptan tablets, sumatriptan nasal spray, and sumatriptan injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular

Hypotension, palpitations

Neurological

Dystonia, tremor

7 DRUG INTERACTIONS

7.1 Ergot-Containing Drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and ZEMBRACE SymTouch within 24 hours of each other is contraindicated.

7.2 Monoamine Oxidase-A Inhibitors

MAO-A inhibitors increase systemic exposure by 2-fold. Therefore, the use of ZEMBRACE SymTouch injection in patients receiving MAO-A inhibitors is contraindicated *[see Clinical Pharmacology (12.3)]*.

7.3 Other 5-HT_1 Agonists

Because their vasospastic effects may be additive, coadministration of ZEMBRACE SymTouch injection and other 5-HT_1 agonists (e.g., triptans) within 24 hours of each other is contraindicated.

7.4 Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of serotonin syndrome have been reported during coadministration of triptans and SSRIs, SNRIs, TCAs, and MAO inhibitors *[see Warnings and Precautions (5.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Data from a prospective pregnancy exposure registry and epidemiological studies of pregnant women have not detected an increased frequency of birth defects or a consistent pattern of birth defects among women exposed to sumatriptan compared with the general population *(see Data)*. In developmental toxicity studies in rats and rabbits, oral administration of sumatriptan to pregnant animals was associated with embryo lethality, fetal abnormalities, and pup mortality. When administered by the intravenous route to pregnant rabbits, sumatriptan was embryo lethal *(see Data)*.

In the U.S. general population, the estimated background risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The reported rate of major birth defects among deliveries to women with migraine ranged from 2.2% to 2.9% and the reported rate of miscarriage was 17%, which were similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Several studies have suggested that women with migraine may be at increased risk of preeclampsia during pregnancy.

Data

Human Data

The Sumatriptan/Naratriptan/Treximet (sumatriptan and naproxen sodium) Pregnancy Registry, a population-based international prospective study, collected data for sumatriptan from January 1996 to September 2012. The Registry documented outcomes of 626 infants and fetuses exposed to sumatriptan during pregnancy (528 with earliest exposure during the first trimester, 78 during the second trimester, 16 during the third trimester, and 4 unknown). The occurrence of major birth defects (excluding fetal deaths and induced abortions without reported defects and all spontaneous pregnancy losses) during first-trimester exposure to sumatriptan was 4.2% (20/478 [95% CI: 2.6% to 6.5%]) and during any trimester of exposure was 4.2% (24/576 [95% CI: 2.7% to 6.2%]). The sample size in this study had 80% power to detect at least a 1.73 to 1.91-fold increase in the rate of major malformations. The number of exposed pregnancy outcomes accumulated during the registry was insufficient to support definitive conclusions about overall malformation risk or for

making comparisons of the frequencies of specific birth defects. Of the 20 infants with reported birth defects after exposure to sumatriptan in the first trimester, 4 infants had ventricular septal defects, including one infant who was exposed to both sumatriptan and naratriptan and 3 infants had pyloric stenosis. No other birth defect was reported for more than 2 infants in this group.

In a study using data from the Swedish Medical Birth Register, live births to women who reported using triptans or ergots during pregnancy were compared with those of women who did not. Of the 2,257 births with first-trimester exposure to sumatriptan, 107 infants were born with malformations (relative risk 0.99 [95% CI: 0.91 to 1.21]). A study using linked data from the Medical Birth Registry of Norway to the Norwegian Prescription Database compared pregnancy outcomes in women who redeemed prescriptions for triptans during pregnancy, as well as a migraine disease comparison group who redeemed prescriptions for sumatriptan before pregnancy only, compared with a population control group. Of the 415 women who redeemed prescriptions for sumatriptan during the first trimester, 15 had infants with major congenital malformations (OR 1.16 [95% CI: 0.69 to 1.94]) while for the 364 women who redeemed prescriptions for sumatriptan before, but not during, pregnancy, 20 had infants with major congenital malformations (OR 1.83 [95% CI: 1.17 to 2.88]), each compared with the population comparison group. Additional smaller observational studies evaluating use of sumatriptan during pregnancy have not suggested an increased risk of teratogenicity.

Animal Data

Oral administration of sumatriptan to pregnant rats during the period of organogenesis resulted in an increased incidence of fetal blood vessel (cervicothoracic and umbilical) abnormalities. The highest no-effect dose for embryofetal developmental toxicity in rats was 60 mg/kg/day. Oral administration of sumatriptan to pregnant rabbits during the period of organogenesis resulted in increased incidences of embryo lethality and fetal cervicothoracic vascular and skeletal abnormalities. Intravenous administration of sumatriptan to pregnant rabbits during the period of organogenesis resulted in an increased incidence of embryo lethality. The highest oral and intravenous no-effect doses for developmental toxicity in rabbits were 15 and 0.75 mg/kg/day, respectively.

Oral administration of sumatriptan to rats prior to and throughout gestation resulted in embryofetal toxicity (decreased body weight, decreased ossification, increased incidence of skeletal abnormalities). The highest no-effect dose was 50 mg/kg/day. In offspring of pregnant rats treated orally with sumatriptan during organogenesis, there was a decrease in pup survival. The highest no-effect dose for this effect was 60 mg/kg/day. Oral treatment of pregnant rats with sumatriptan during the latter part of gestation and throughout lactation resulted in a decrease in pup survival. The highest no-effect dose for this finding was 100 mg/kg/day.

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 ZEMBRACE SymTouch 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 ZEMBRACE SymTouch.

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 in pediatric patients have not been established. ZEMBRACE SymTouch injection is not recommended for use in patients younger than 18 years of age.

Two controlled clinical trials evaluated sumatriptan nasal spray (5 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 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 injection 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 ZEMBRACE SymTouch injection *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

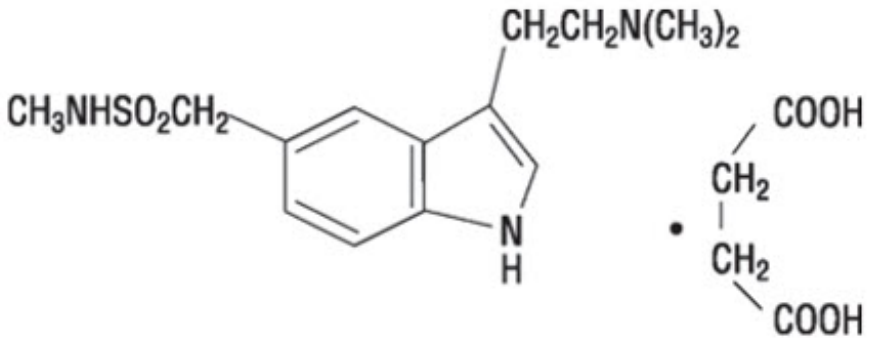
Coronary vasospasm was observed after intravenous administration of sumatriptan injection *[see Contraindications (4)]*. Overdoses would be expected from animal data (dogs at 0.1 g/kg, rats at 2 g/kg) to possibly cause convulsions, tremor, inactivity, erythema of the extremities, reduced respiratory 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 ZEMBRACE SymTouch injection 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

ZEMBRACE SymTouch injection contains sumatriptan succinate, a selective 5-$HT_{1B/1D}$ receptor agonist. Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino) ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1), and it has the following structure:



The empirical formula is $C_{14}H_{21}N_3O_2S \bullet C_4H_6O_4$, representing a molecular weight of 413.5. Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline.

ZEMBRACE SymTouch is a clear, colorless to pale yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 0.5 mL of ZEMBRACE SymTouch contains 4.2 mg of sumatriptan succinate equivalent to 3 mg of sumatriptan (base) and 4.15 mg of sodium chloride, USP in Water for Injection, USP.

The pH range of solution is approximately 4.2 to 5.3 and the osmolality of injection is approximately 291 mOsmol (275 to 315 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

After a single 3 mg dose, ZEMBRACE SymTouch was bioequivalent to IMITREX subcutaneous injection.

Absorption and Bioavailability: The bioavailability of sumatriptan via subcutaneous site injection to 18 healthy male subjects was 97% ± 16% of that obtained following intravenous injection.

After a single 6-mg subcutaneous manual injection into the deltoid area of the arm in 18 healthy males (age: 24 ± 6 years, weight: 70 kg), the maximum serum concentration (C_{max}) of sumatriptan was (mean ± standard deviation) 74 ± 15 ng/mL and the time to peak concentration (T_{max}) was 12 minutes after injection (range: 5 to 20 minutes). In this trial, the same dose injected subcutaneously in the thigh gave a C_{max} of 61 ± 15 ng/mL by manual injection versus 52 ±15 ng/mL by auto-injector techniques. The T_{max} or amount absorbed was not significantly altered by either the site or technique of injection.

Distribution: 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.

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.

Elimination: 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 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 ZEMBRACE SymTouch injection in this population is contraindicated *[see Contraindications (4)]*.

Race: The systemic clearance and C_{max} of subcutaneous sumatriptan were similar in black (n = 34) and Caucasian (n = 38) healthy male subjects.

Drug Interaction Studies:

Monoamine Oxidase-A Inhibitors: In a trial of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of 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 high dose in rat was reduced from 360 mg/kg/day during Week 21). The highest dose tested in mice and rats was approximately 130 and 260 times, respectively, the single MRHD of 6 mg administered subcutaneously on a mg/m^2 basis. 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, or 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; however, the relative plasma exposure at the lowest dose tested was approximately 3 times the human exposure after a 6-mg subcutaneous dose.

14 CLINICAL STUDIES

Clinical Studies with Sumatriptan Injection

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*				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	13	37	50	57	80
6 mg	10	63	73	70	83
8 mg	23	57	80	83	93

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

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

1-Hour Data	Study 2		Study 3	
	Placebo (n = 190)	Sumatriptan 6 mg (n = 384)	Placebo (n = 180)	Sumatriptan 6 mg (n = 350)
Subjects with pain relief (grade 0/1)	18%	70%*	26%	70%*
Subjects with no pain	5%	48%*	13%	49%*
Subjects without nausea	48%	73%*	50%	73%*
Subjects without photophobia	23%	56%*	25%	58%*
Subjects with little or no clinical disability†	34%	76%*	34%	76%*
2-Hour Data	Study 2		Study 3	
	Placebo‡	Sumatriptan 6 mg§	Placebo‡	Sumatriptan 6 mg§
Subjects with pain relief (grade 0/1)	31%	81%*	39%	82%*
Subjects with no pain	11%	63%*	19%	65%*
Subjects without nausea	56%	82%*	63%	81%*
Subjects without photophobia	31%	72%*	35%	71%*
Subjects with little or no clinical disability†	42%	85%*	49%	84%*

* $P<0.05$ versus placebo.
† A successful outcome in terms of clinical disability was defined prospectively as ability to work mildly impaired or ability to work and function normally.
‡ Includes patients that may have received an additional placebo injection 1 hour after the initial injection.
§ 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 injections was unaffected by whether or not the migraine was associated with aura, duration of attack, gender or age of the subject, or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers).

Clinical Study with ZEMBRACE SymTouch

In a double-blind, randomized, placebo-controlled clinical trial of ZEMBRACE SymTouch, 230 patients with migraine with or without aura received either ZEMBRACE SymTouch

(N=111) or placebo (N=119) for a single migraine attack. The patients had a mean age of 41 years (range 18 to 65 years); approximately 76% were White and 85% were female.

The study excluded patients with medication overuse headache, treatment with onabotulinumtoxin A within 180 days, and patients with a history of cluster headache.

The primary efficacy endpoint was the proportion of patients who were pain-free (defined as a reduction from pre-dose moderate [Grade 2] or severe [Grade 3] pain to none [Grade 0]) 2 hours after the first dose. Of the ZEMBRACE SymTouch-treated patients, 46% were pain free at 2 hours after treatment compared to 27% of the placebo-treated patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

- ZEMBRACE® SymTouch® 3 mg/0.5 mL Injection contains sumatriptan as the succinate salt and is supplied as a clear, colorless to pale yellow, sterile, nonpyrogenic solution in a prefilled, ready-to-use, single dose, disposable auto-injector unit (NDC # 70792-809-89).
- Each carton contains 4 units (NDC # 70792-809-38) 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 to 15° to 30°C (59° to 86°F). Protect from light.

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 ZEMBRACE SymTouch injection 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 injection. 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 ZEMBRACE SymTouch injection within 24 hours of another triptan or an ergot-type medication (including dihydroergotamine or methylsergide) 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 ZEMBRACE SymTouch injection 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 ZEMBRACE SymTouch injection may cause somnolence and dizziness; instruct patients to evaluate their ability to perform complex tasks during migraine attacks and after administration of ZEMBRACE SymTouch injection.

How to Use ZEMBRACE SymTouch

Provide patients instruction on the proper use of ZEMBRACE SymTouch injection if they are able to self-administer ZEMBRACE SymTouch injection in medically unsupervised conditions.

Inform patients that the needle in the ZEMBRACE SymTouch penetrates approximately ¼ of an inch (6 mm). Inform patients that the injection is intended to be given subcutaneously and intramuscular or intravascular delivery should be avoided. Instruct patients to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle.

Manufactured for
TONIX MEDICINES, INC.
Chatham, NJ 07928

ZEMBRACE and SymTouch are registered trademarks of Tonix Medicines, Inc.

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

Revised: 11/2023

Patient Information
ZEMBRACE® SymTouch® (Zem-brace Sim-Touch)
(sumatriptan succinate)
Injection

What is the most important information I should know about ZEMBRACE SymTouch?

ZEMBRACE SymTouch can cause serious side effects, including:

Heart attack and other heart problems. Heart problems may lead to death. Stop taking ZEMBRACE SymTouch and get emergency medical help right away if you have any of the following symptoms of a heart attack:

- discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw, or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded

ZEMBRACE SymTouch is not for people with risk factors for heart disease unless a heart exam is done and shows no problem. You have a higher risk for heart disease if you:

- have high blood pressure
- have high cholesterol levels
- smoke
- are overweight
- have diabetes
- have a family history of heart disease

What is ZEMBRACE SymTouch?

ZEMBRACE SymTouch is a prescription medicine used to treat acute migraine headaches with or without aura in adults who have been diagnosed with migraine.

ZEMBRACE SymTouch is not used to treat other types of headaches such as hemiplegic (that make you unable to move on one side of your body) or basilar (rare form of migraine with aura) migraines.

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

It is not known if ZEMBRACE SymTouch is safe and effective in children under 18 years of age.

Who should not take ZEMBRACE SymTouch?

Do not take ZEMBRACE SymTouch if you have:

- heart problems or a history of heart problems
- narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular disease)
- uncontrolled high blood pressure
- hemiplegic migraines or basilar migraines. If you are not sure if you have these types of migraines, ask your healthcare provider.
- had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation

- severe liver problems
- an allergy to sumatriptan or any of the ingredients in ZEMBRACE SymTouch. See the end of this leaflet for a complete list of ingredients in ZEMBRACE SymTouch.
- taken any of the following medicines in the last 24 hours:
  - almotriptan
  - eletriptan
  - frovatriptan
  - naratriptan
  - rizatriptan
  - ergotamines
  - dihydroergotamine

Ask your healthcare provider if you are not sure if your medicine is listed above.

What should I tell my healthcare provider before taking ZEMBRACE SymTouch?

Before taking ZEMBRACE SymTouch, tell your healthcare provider about all of your medical conditions, including if you:

- have high blood pressure
- have high cholesterol
- have diabetes
- smoke
- are overweight
- have heart problems or family history of heart problems or stroke
- have kidney problems
- have liver problems
- have had epilepsy or seizures
- are not using effective birth control
- are pregnant or plan to become pregnant. It is not known if ZEMBRACE SymTouch can harm your unborn baby.
- are breastfeeding or plan to breastfeed. ZEMBRACE SymTouch passes into your breast milk. It is not known if this can harm your baby. Talk with your healthcare provider about the best way to feed your baby if you take ZEMBRACE SymTouch.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Using ZEMBRACE SymTouch with certain other medicines can affect each other, causing serious side effects.

Especially tell your healthcare provider if you take anti-depressant medicines called:

- selective serotonin reuptake inhibitors (SSRIs)
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants (TCAs)
- monoamine oxidase inhibitors (MAOIs)

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take ZEMBRACE SymTouch?

- Certain people should take their first dose of ZEMBRACE SymTouch in their healthcare provider's office or in another medical setting. Ask your healthcare provider if you should take your first dose in a medical setting.
- Use ZEMBRACE SymTouch exactly as your healthcare provider tells you to use it.
- Your healthcare provider may change your dose. Do not change your dose without first talking with your healthcare provider.
- For adults, the usual dose is a single injection given just below the skin.
- You should give an injection as soon as the symptoms of your headache start, but it may be given at any time during a migraine headache attack.
- If you did not get any relief after the first injection, do not give a second injection without first talking with your healthcare provider.
- You may use a second dose of ZEMBRACE SymTouch after the first dose of ZEMBRACE SymTouch OR after one dose of another sumatriptan medication separated by at least 1 hour, but not sooner, if your headache comes back or you only get some relief after your first injection.
- Do not take more than a total of 12 mg of ZEMBRACE SymTouch in a 24-hour period. Talk to your doctor about how many ZEMBRACE SymTouch you can take in a 24-hour period if you take another form of sumatriptan medication in between ZEMBRACE SymTouch.
- If you use too much ZEMBRACE SymTouch, call your healthcare provider or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you take ZEMBRACE SymTouch so you can talk with your healthcare provider about how ZEMBRACE SymTouch is working for you.

What should I avoid while taking ZEMBRACE SymTouch?

ZEMBRACE SymTouch can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not drive a car, use machinery, or do anything where you need to be alert.

What are the possible side effects of ZEMBRACE SymTouch?

See "What is the most important information I should know about ZEMBRACE SymTouch?"

ZEMBRACE SymTouch may cause serious side effects, including:

- **changes in color or sensation in your fingers and toes (Raynaud's syndrome)**
- **stomach and intestinal problems** (gastrointestinal and colonic ischemic events). Symptoms of gastrointestinal and colonic ischemic events include:
  - sudden or severe stomach pain
  - stomach pain after meals
  - weight loss
  - nausea or vomiting
  - constipation or diarrhea
  - bloody diarrhea
  - fever
- **problems with blood circulation to your legs and feet (peripheral vascular ischemia).** Symptoms of peripheral vascular ischemia include:
  - cramping and pain in your legs or hips
  - feeling of heaviness or tightness in your leg muscles
  - burning or aching pain in your feet or toes while resting

- numbness, tingling, or weakness in your legs
- cold feeling or color changes in 1 or both legs or feet

- **hives (itchy bumps); swelling of your tongue, mouth, or throat.**
- **medication overuse headaches.** Some people who use too many ZEMBRACE SymTouch injections may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with ZEMBRACE SymTouch.
- **serotonin syndrome**. Serotonin syndrome is a rare but serious problem that can happen in people using ZEMBRACE SymTouch, especially if ZEMBRACE SymTouch is used with anti-depressant medicines called SSRIs or SNRIs. Call your healthcare provider right away if you have any of the following symptoms of serotonin syndrome:
  - mental changes such as seeing things that are not there (hallucinations), agitation, or coma
  - fast heartbeat
  - changes in blood pressure
  - high body temperature
  - tight muscles
  - trouble walking
- **seizures**. Seizures have happened in people taking ZEMBRACE SymTouch who have never had seizures before. Talk with your healthcare provider about your chance of having seizures while you take ZEMBRACE SymTouch.

The most common side effects of ZEMBRACE SymTouch include:
- pain or redness at your injection site
- tingling or numbness in your fingers or toes
- dizziness
- warm, hot, burning feeling to your face (flushing)
- discomfort or stiffness in your neck
- feeling weak, drowsy, or tired

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 ZEMBRACE SymTouch. 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 ZEMBRACE SymTouch?
- Store between 68° to 77°F (20° to 25°C)
- Store your medicine away from light.
- Keep your medicine in the packaging or carrying case provided with it.

Keep ZEMBRACE SymTouch and all medicines out of the reach of children.

General information about the safe and effective use of ZEMBRACE SymTouch.
Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use ZEMBRACE SymTouch for a condition for which it was not prescribed. Do not give ZEMBRACE SymTouch to other people, even if they have the same symptoms you have. It may harm them.
This Patient Information leaflet summarizes the most important information about

ZEMBRACE SymTouch. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ZEMBRACE SymTouch that is written for healthcare professionals.
For more information, go to www.Zembrace.com or call 1-888-869-7633 (1-888-TNXPMED).

What are the ingredients in ZEMBRACE SymTouch Injection?
Active ingredient: sumatriptan succinate
Inactive ingredients: sodium chloride, water for injection
Manufactured for
TONIX MEDICINES, INC.
Chatham, NJ 07928
ZEMBRACE and SymTouch are registered trademarks of Tonix Medicines, Inc.
This product may be covered by one or more U.S. patent(s).

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

Revised: 11/2023

TOSYMRA- sumatriptan spray
Tonix Medicines, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TOSYMRA® safely and effectively. See full prescribing information for TOSYMRA®.

TOSYMRA® (sumatriptan) nasal spray
Initial U.S. Approval: 1992

INDICATIONS AND USAGE

TOSYMRA is a serotonin (5-$HT_{1B/1D}$) receptor agonist (triptan) indicated for the acute treatment of migraine with or without aura in adults (1)

Limitations of Use:

- Use only if a clear diagnosis of migraine has been established (1)
- Not indicated for the preventive treatment of migraine (1)
- Not indicated for the treatment of cluster headache (1)

DOSAGE AND ADMINISTRATION

- Single dose of 10 mg of nasal spray (2)
- Maximum dose in a 24-hour period: 30 mg; separate doses by at least one hour (2)

DOSAGE FORMS AND STRENGTHS

Nasal Spray, 10 mg (3)

CONTRAINDICATIONS

- History of coronary artery disease or coronary vasospasm (4)
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders (4)
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine (4)
- Peripheral vascular disease (4)
- Ischemic bowel disease (4)
- Uncontrolled hypertension (4)
- Recent (within 24 hours) use of another 5-HT_1 agonist (e.g., another triptan) or of an ergotamine-containing medication (4)
- Concurrent or recent (past 2 weeks) use of monoamine oxidase-A inhibitor (4)
- Hypersensitivity to sumatriptan (angioedema and anaphylaxis seen) (4)
- Severe hepatic impairment (4)

WARNINGS AND PRECAUTIONS

- Myocardial ischemia/infarction and Prinzmetal's angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors (5.1)
- Arrhythmias: Discontinue TOSYMRA if occurs (5.2)
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness: Generally, not associated with myocardial ischemia; evaluate for coronary artery disease in patients at high risk (5.3)
- Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Discontinue TOSYMRA if occurs (5.4)
- Gastrointestinal ischemia and reactions, peripheral vasospastic reactions: Discontinue TOSYMRA if occurs (5.5)
- Medication overuse headache: Detoxification may be necessary (5.6)
- Serotonin syndrome: Discontinue TOSYMRA if occurs (5.7)
- Increase in blood pressure: Hypertensive crisis can occur (5.8)
- Hypersensitivity reactions: Angioedema and anaphylaxis can occur (5.9)
- Seizures: Use with caution in patients with epilepsy or a lowered seizure threshold (5.10)
- Local irritation: Burning and abnormal taste can occur (5.11)

ADVERSE REACTIONS

Most common adverse reactions (≥5% and > placebo) with sumatriptan injection were tingling, dizziness/vertigo, warm/hot sensation, burning sensation, feeling of heaviness, pressure sensation, flushing, feeling of tightness, and numbness (6.1)

Additional common adverse reactions with TOSYMRA include application site reactions, dysgeusia, and throat irritation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Tonix Medicines, Inc. at 1-888-869-7633 (1-888-TNXPMED) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TOSYMRA is indicated for the acute treatment of migraine with or without aura in adults.

Limitations of Use:

- Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated with TOSYMRA, reconsider the diagnosis before TOSYMRA is administered to treat any subsequent attacks.
- TOSYMRA is not indicated for the preventive treatment of migraine.
- TOSYMRA is not indicated for the treatment of cluster headache.

2 DOSAGE AND ADMINISTRATION

The recommended dose of TOSYMRA is 10 mg given as a single spray in one nostril.

The maximum cumulative dose that may be given in a 24-hour period is 30 mg, with doses of TOSYMRA separated by at least 1 hour. TOSYMRA may also be given at least 1 hour following a dose of another sumatriptan product.

3 DOSAGE FORMS AND STRENGTHS

Single-dose nasal spray device delivering 10 mg of sumatriptan.

4 CONTRAINDICATIONS

TOSYMRA 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 *[see Warnings and Precautions (5.1)]*.
- Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders *[see Warnings and Precautions (5.2)]*.
- History of stroke or transient ischemic attack (TIA) or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke *[see Warnings and Precautions (5.4)]*.

- Peripheral vascular disease *[see Warnings and Precautions (5.5)]*.
- Ischemic bowel disease *[see Warnings and Precautions (5.5)]*.
- Uncontrolled hypertension *[see Warnings and Precautions (5.8)]*.
- Recent use (i.e., within 24 hours) of ergotamine-containing medication, ergot-type medication (such as dihydroergotamine or methysergide), or another 5-hydroxytryptamine$_1$ (5-HT$_1$) agonist *[see Drug Interactions (7.1, 7.3)]*.
- Concurrent administration of a monoamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.
- Hypersensitivity to sumatriptan (angioedema and anaphylaxis seen) *[see Warnings and Precautions (5.9)]*.
- Severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina

The use of TOSYMRA is contraindicated in patients with ischemic or vasospastic CAD. There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of sumatriptan. Some of these reactions occurred in patients without known CAD. 5-HT$_1$ agonists, including TOSYMRA, may cause coronary artery vasospasm (Prinzmetal's angina), even in patients without a history of CAD.

Perform a cardiovascular evaluation in triptan-naive patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving TOSYMRA. If there is evidence of CAD or coronary artery vasospasm, TOSYMRA is contraindicated. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first dose of TOSYMRA in a medically supervised setting and performing an electrocardiogram (ECG) immediately following administration of TOSYMRA. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of TOSYMRA.

5.2 Arrhythmias

Life-threatening disturbances of cardiac rhythm, including ventricular tachycardia and ventricular fibrillation leading to death, have been reported within a few hours following the administration of 5-HT$_1$ agonists. Discontinue TOSYMRA if these disturbances occur.

TOSYMRA is contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.

5.3 Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure

Sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw commonly occur after treatment with sumatriptan injection and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. The use of TOSYMRA is contraindicated in patients shown to have CAD and those with Prinzmetal's variant angina.

5.4 Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT_1 agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. Also, patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). Discontinue TOSYMRA if a cerebrovascular event occurs.

Before treating headaches in patients not previously diagnosed with migraine or in patients who present with atypical symptoms, exclude other potentially serious neurological conditions. TOSYMRA is contraindicated in patients with a history of stroke or TIA.

5.5 Other Vasospasm Reactions

TOSYMRA may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with abdominal pain and bloody diarrhea), splenic infarction, and Raynaud's syndrome. In patients who experience symptoms or signs suggestive of non-coronary vasospasm reaction following the use of any 5-HT_1 agonist, rule out a vasospastic reaction before receiving additional TOSYMRA.

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT_1 agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT_1 agonists have not been clearly established.

5.6 Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or combination of these drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches, or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

5.7 Serotonin Syndrome

Serotonin syndrome may occur with TOSYMRA, particularly during co-administration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors *[see Drug Interactions (7.4)]*. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. Discontinue TOSYMRA if serotonin syndrome is suspected.

5.8 Increase in Blood Pressure

Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has been reported on rare occasions in patients treated with 5-HT_1 agonists, including patients without a history of hypertension. Monitor blood pressure in patients treated with TOSYMRA. TOSYMRA is contraindicated in patients with uncontrolled hypertension.

5.9 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema and anaphylaxis, 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. TOSYMRA is contraindicated in patients with a history of hypersensitivity reaction to sumatriptan.

5.10 Seizures

Seizures have been reported following administration of sumatriptan. Some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. There are also reports in patients where no such predisposing factors are apparent. TOSYMRA should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

5.11 Local Irritation

Local irritative symptoms were reported in approximately 46% of patients treated with TOSYMRA in an open-label trial which allowed repeated use of TOSYMRA over the course of 6 months. Of these, the most common local irritative symptoms were application site reaction (36%), dysgeusia (21%), and throat irritation (5%). Approximately 0.5% of the cases were reported as severe.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina *[see Warnings and Precautions (5.1)]*
- Arrhythmias *[see Warnings and Precautions (5.2)]*
- Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure *[see Warnings and Precautions (5.3)]*
- Cerebrovascular Events *[see Warnings and Precautions (5.4)]*
- Other Vasospasm Reactions *[see Warnings and Precautions (5.5)]*
- Medication Overuse Headache *[see Warnings and Precautions (5.6)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.7)]*
- Increase in Blood Pressure *[see Warnings and Precautions (5.8)]*
- Hypersensitivity Reactions *[see Contraindications (4), Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*
- Local Irritation *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Placebo-Controlled Trials with Sumatriptan Injection

Table 1 lists adverse reactions that occurred in 2 placebo-controlled clinical trials in patients with migraine (Studies 2 and 3) following either a single 6 mg dose of sumatriptan injection or placebo. Only reactions that occurred at a frequency of 2% or more in groups treated with sumatriptan injection 6 mg and that occurred at a frequency greater than the placebo group are included in Table 1.

Table 1: Adverse Reactions in Pooled Placebo-Controlled Trials in Patients with Migraine (Studies 2 and 3)

Adverse Reaction	Sumatriptan Injection 6 mg Subcutaneous (n = 547) %	Placebo (n = 370) %
Atypical sensations	42	9
Tingling	14	3
Warm/hot sensation	11	4
Burning sensation	7	<1
Feeling of heaviness	7	1
Pressure sensation	7	2
Feeling of tightness	5	<1
Numbness	5	2
Feeling strange	2	<1
Tight feeling in head	2	<1
Cardiovascular		
Flushing	7	2
Chest discomfort	5	1
Tightness in chest	3	<1
Pressure in chest	2	<1
Ear, nose, and throat		
Throat discomfort	3	<1
Discomfort: nasal cavity/sinuses	2	<1
Miscellaneous		
Jaw discomfort	2	0
Musculoskeletal		
Weakness	5	<1
Neck pain/stiffness	5	<1
Myalgia	2	<1
Neurological		
Dizziness/vertigo	12	4
Drowsiness/sedation	3	2

Headache	2	<1
Skin		
Sweating	2	1

The incidence of adverse reactions in controlled clinical trials was not affected by gender or age of the patients. There were insufficient data to assess the impact of race on the incidence of adverse reactions.

Adverse Reactions in Studies with TOSYMRA

In an open-label study that was designed to evaluate the local tolerability of TOSYMRA, repeated use of TOSYMRA was allowed over the course of 6 months. In this study, local irritative symptoms were reported in approximately 46% of patients treated with TOSYMRA, the most common of which were application site reactions (e.g., burning sensations in the nose), dysgeusia, and throat irritation *[see Warnings and Precautions (5.11)]*.

6.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of sumatriptan tablets, sumatriptan nasal spray, and sumatriptan injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular:

Hypotension, palpitations.

Neurological:

Dystonia, tremor.

7 DRUG INTERACTIONS

7.1 Ergot-Containing Drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and TOSYMRA within 24 hours of each other is contraindicated.

7.2 Monoamine Oxidase-A Inhibitors

MAO-A inhibitors increase systemic exposure by 2-fold. Therefore, the use of TOSYMRA in patients receiving MAO-A inhibitors is contraindicated *[see Clinical Pharmacology (12.3)]*.

7.3 Other 5-HT_1 Agonists

Because their vasospastic effects may be additive, coadministration of TOSYMRA and other 5-HT_1 agonists (e.g., triptans) within 24 hours of each other is contraindicated.

7.4 Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of serotonin syndrome have been reported during co-administration of triptans and SSRIs, SNRIs, TCAs, and MAO inhibitors *[see Warnings and Precautions (5.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Data from a prospective pregnancy exposure registry and epidemiological studies of pregnant women have not detected an increased frequency of birth defects or a consistent pattern of birth defects among women exposed to sumatriptan compared with the general population *(see Data)*. In developmental toxicity studies in rats and rabbits, oral administration of sumatriptan to pregnant animals was associated with embryo lethality, fetal abnormalities, and pup mortality. When administered by the intravenous route to pregnant rabbits, sumatriptan was embryo lethal *(see Data)*.

In the U.S. general population, the estimated background risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The reported rate of major birth defects among deliveries to women with migraine ranged from 2.2% to 2.9% and the reported rate of miscarriage was 17%, which were similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Several studies have suggested that women with migraine may be at increased risk of preeclampsia during pregnancy.

Data

Human Data

The Sumatriptan/Naratriptan/Treximet (sumatriptan and naproxen sodium) Pregnancy Registry, a population-based international prospective study, collected data for sumatriptan from January 1996 to September 2012. The Registry documented outcomes of 626 infants and fetuses exposed to sumatriptan during pregnancy (528 with earliest exposure during the first trimester, 78 during the second trimester, 16 during the third trimester, and 4 unknown). The occurrence of major birth defects (excluding fetal deaths and induced abortions without reported defects and all spontaneous pregnancy losses) during first-trimester exposure to sumatriptan was 4.2% (20/478 [95% CI: 2.6% to 6.5%]) and during any trimester of exposure was 4.2% (24/576 [95% CI: 2.7% to 6.2%]). The sample size in this study had 80% power to detect at least a 1.73- to 1.91-fold increase in the rate of major malformations. The number of exposed pregnancy outcomes accumulated during the registry was insufficient to support definitive conclusions about overall malformation risk or for making comparisons of the frequencies of specific birth defects. Of the 20 infants with reported birth defects after exposure to sumatriptan in the first trimester, 4 infants had ventricular septal defects, including one infant who was exposed to both sumatriptan and naratriptan, and 3 infants had pyloric stenosis. No other birth defect was reported for more than 2 infants in this group.

In a study using data from the Swedish Medical Birth Register, live births to women who reported using triptans or ergots during pregnancy were compared with those of women who did not. Of the 2,257 births with first-trimester exposure to sumatriptan, 107 infants were born with malformations (relative risk 0.99 [95% CI: 0.91 to 1.21]). A study using linked data from the Medical Birth Registry of Norway to the Norwegian Prescription Database compared pregnancy outcomes in women who redeemed prescriptions for triptans during pregnancy, as well as a migraine disease comparison group who redeemed prescriptions for sumatriptan before pregnancy only, compared with a population control group. Of the 415 women who redeemed prescriptions for sumatriptan during the first trimester, 15 had infants with major congenital malformations (OR 1.16 [95% CI: 0.69 to 1.94]) while for the 364 women who redeemed prescriptions for sumatriptan before, but not during, pregnancy, 20 had infants with major congenital malformations (OR 1.83 [95% CI: 1.17 to 2.88]), each compared with the population comparison group. Additional smaller observational studies evaluating use of sumatriptan during pregnancy have not suggested an increased risk of teratogenicity.

Animal Data

Oral administration of sumatriptan to pregnant rats during the period of organogenesis resulted in an increased incidence of fetal blood vessel (cervicothoracic and umbilical) abnormalities. The highest no-effect dose for embryofetal developmental toxicity in rats was 60 mg/kg/day. Oral administration of sumatriptan to pregnant rabbits during the period of organogenesis resulted in increased incidences of embryo lethality and fetal cervicothoracic vascular and skeletal abnormalities. Intravenous administration of sumatriptan to pregnant rabbits during the period of organogenesis resulted in an increased incidence of embryo lethality. The highest oral and intravenous no-effect doses for developmental toxicity in rabbits were 15 and 0.75 mg/kg/day, respectively.

Oral administration of sumatriptan to rats prior to and throughout gestation resulted in embryofetal toxicity (decreased body weight, decreased ossification, increased incidence of skeletal abnormalities). The highest no-effect dose was 50 mg/kg/day. In offspring of pregnant rats treated orally with sumatriptan during organogenesis, there was a decrease in pup survival. The highest no-effect dose for this effect was 60 mg/kg/day. Oral treatment of pregnant rats with sumatriptan during the latter part of gestation and throughout lactation resulted in a decrease in pup survival. The highest no-effect dose for this finding was 100 mg/kg/day.

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,

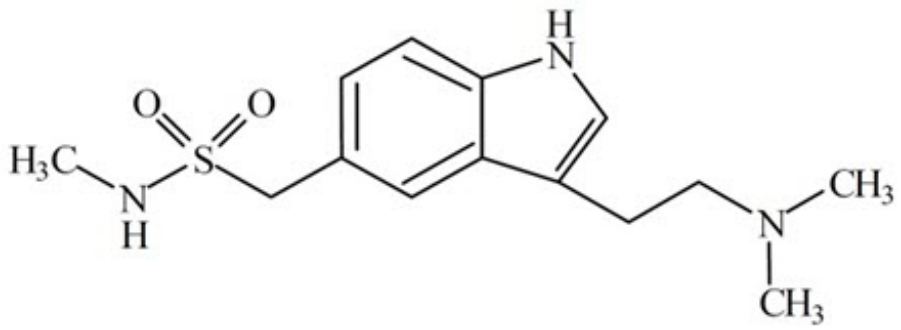
erythema of the extremities, reduced respiratory rate, cyanosis, ataxia, mydriasis, injection site reactions (desquamation, hair loss, and scab formation), and paralysis.

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 $C_{14}H_{21}N_3O_2S$, 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 uL 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

Monoamine 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*				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†	**13**	**37**	**50**	**57**	**80**
6 mg	10	63	73	70	83

8 mg	23	57	80	83	93

* Relief is defined as the reduction of moderate or severe pain to no or mild pain after dosing without use of rescue medication.
† 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**	
1-Hour Data	**Placebo (n = 190)**	**Sumatriptan Injection 6 mg (n = 384)**	**Placebo (n = 180)**	**Sumatriptan Injection 6 mg (n = 350)**
Patients with pain relief (Grade 0/1)	18%	70%*	26%	70%*
Patients with no pain	5%	48%*	13%	49%*
Patients without nausea	48%	73%*	50%	73%*
Patients without photophobia	23%	56%*	25%	58%*
Patients with little or no clinical disability†	34%	76%*	34%	76%*
	Study 2		**Study 3**	
2-Hour Data	**Placebo‡**	**Sumatriptan Injection 6 mg§**	**Placebo‡**	**Sumatriptan Injection 6 mg§**
Patients with pain relief (Grade 0/1)	31%	81%*	39%	82%*
Patients with no pain	11%	63%*	19%	65%*
Patients without nausea	56%	82%*	63%	81%*
Patients without photophobia	31%	72%*	35%	71%*
Patients with little or no clinical disability†	42%	85%*	49%	84%*

* P<0.05 versus placebo.
† A successful outcome in terms of clinical disability was defined prospectively as ability to work mildly impaired or ability to work and function normally.
‡ Includes patients that may have received an additional placebo injection 1 hour after the initial injection.

§ 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 70792-812-89) contains sumatriptan and is supplied as a ready-to-use, single-dose, disposable unit.
- Each carton contains 6 units (NDC 70792-812-61) 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 methylsergide) 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
TONIX MEDICINES, INC..Chatham, NJ 07928

TOSYMRA is a registered trademark of Tonix Medicines, Inc.

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

Revised: 10/2023

Patient Information
TOSYMRA® (toe-SIM-ruh)
(sumatriptan)
Nasal Spray

What is the most important information I should know about TOSYMRA?
TOSYMRA can cause serious side effects, including:
Heart attack and other heart problems. Heart problems may lead to death. Stop taking TOSYMRA and get emergency medical help right away if you have any of the following symptoms of a heart attack:

- discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw, or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded

TOSYMRA is not for people with risk factors for heart disease unless a heart exam is done and shows no problem. You have a higher risk for heart disease if you:

- have high blood pressure
- have high cholesterol levels
- smoke
- are overweight
- have diabetes
- have a family history of heart disease

What is TOSYMRA?

TOSYMRA is a prescription medicine used to treat acute migraine headaches with or without aura in adults.

TOSYMRA is not used to treat other types of headaches such as hemiplegic (that make you unable to move on one side of your body) or basilar (rare form of migraine with aura) migraines.

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

TOSYMRA is not used to treat cluster headaches.

It is not known if TOSYMRA is safe and effective in children under 18 years of age.

Do not take TOSYMRA if you have:

- heart problems or a history of heart problems
- narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular disease)
- uncontrolled high blood pressure
- severe liver problems
- hemiplegic migraines or basilar migraines. If you are not sure if you have these types of migraines, ask your healthcare provider.
- had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation
- taken any of the following medicines in the last 24 hours:
  - almotriptan
  - eletriptan
  - frovatriptan
  - naratriptan
  - rizatriptan
  - ergotamines
  - dihydroergotamine

  Ask your healthcare provider if you are not sure if your medicine is listed above.

- are taking certain antidepressants, known as monoamine oxidase (MAO)-A inhibitors or it has been 2 weeks or less since you stopped taking a MAO-A inhibitor. Ask your

healthcare provider or pharmacist for a list of these medicines if you are not sure.
- an allergy to sumatriptan or any of the ingredients in TOSYMRA. See the end of this Patient Information leaflet for a complete list of ingredients in TOSYMRA.

Before taking TOSYMRA, tell your healthcare provider about all of your medical conditions, including if you:
- have high blood pressure.
- have high cholesterol.
- have diabetes.
- smoke.
- are overweight.
- have heart problems or family history of heart problems or stroke.
- have kidney problems.
- have liver problems.
- have had epilepsy or seizures.
- are not using effective birth control.
- are pregnant or plan to become pregnant. It is not known if TOSYMRA can harm your unborn baby.
- are breastfeeding or plan to breastfeed. TOSYMRA passes into your breast milk. It is not known if this can harm your baby. Talk with your healthcare provider about the best way to feed your baby if you take TOSYMRA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TOSYMRA and certain other medicines can affect each other, causing serious side effects.
Especially tell your healthcare provider if you take anti-depressant medicines called:
- selective serotonin reuptake inhibitors (SSRIs)
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants (TCAs)
- monoamine oxidase inhibitors (MAOIs)

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.
Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take TOSYMRA?
- See the Instructions for Use for complete information on how to use TOSYMRA nasal spray.
- Certain people should take their first dose of TOSYMRA in their healthcare provider's office or in another medical setting. Ask your healthcare provider if you should take your first dose in a medical setting.
- Use TOSYMRA exactly as your healthcare provider tells you to use it.
- You should take TOSYMRA as soon as the symptoms of your headache start, but it may be taken at any time during a migraine.
- If your headache comes back after the first nasal spray or you only get some relief from your headache, you can use a second nasal spray 1 hour after the first nasal spray.

- Do not use more than 30 mg of TOSYMRA Nasal Spray in a 24-hour period.
- If you use too much TOSYMRA, call your healthcare provider or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you take TOSYMRA, so you can talk with your healthcare provider about how TOSYMRA is working for you.

What should I avoid while taking TOSYMRA?

TOSYMRA can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not drive a car, use machinery, or do anything where you need to be alert.

What are the possible side effects of TOSYMRA?

TOSYMRA may cause serious side effects. See "What is the most important information I should know about TOSYMRA?"

These serious side effects include:

- changes in color or sensation in your fingers and toes (Raynaud's syndrome)
- stomach and intestinal problems (gastrointestinal and colonic ischemic events). Symptoms of gastrointestinal and colonic ischemic events include:
  - sudden or severe stomach pain
  - stomach pain after meals
  - weight loss
  - nausea or vomiting
  - constipation or diarrhea
  - bloody diarrhea
  - fever
- problems with blood circulation to your legs and feet (peripheral vascular ischemia). Symptoms of peripheral vascular ischemia include:
  - cramping and pain in your legs or hips
  - feeling of heaviness or tightness in your leg muscles
  - burning or aching pain in your feet or toes while resting
  - numbness, tingling, or weakness in your legs
  - cold feeling or color changes in 1 or both legs or feet
- medication overuse headaches. Some people who use too much migraine medicine, such as TOSYMRA, for 10 or more days each month may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with TOSYMRA.
- serotonin syndrome. Serotonin syndrome is a rare but serious problem that can happen in people using TOSYMRA, especially if TOSYMRA is used with anti-depressant medicines called SSRIs or SNRIs. Call your healthcare provider right away if you have any of the following symptoms of serotonin syndrome:
  - mental changes such as seeing things that are not there (hallucinations), agitation, or coma
  - fast heartbeat
  - changes in blood pressure
  - high body temperature
  - tight muscles
  - trouble walking
- increased blood pressure including a sudden severe increase (hypertensive crisis) even if you have no history of high blood pressure.
- hives (itchy bumps); swelling of your tongue, mouth, or throat.
- seizures. Seizures have happened in people taking TOSYMRA who have never had

seizures before. Talk with your healthcare provider about your chance of having seizures while you take TOSYMRA.

The most common side effects of TOSYMRA include:

- tingling
- feeling of heaviness
- numbness
- dizziness
- feeling of pressure
- application site (nasal) reactions
- feeling warm or hot
- flushing
- abnormal taste
- burning feeling
- feeling of tightness
- 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.TOSYMRA.com or call 1-888-869-7633 (1-888-TNXPMED).

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
TONIX MEDICINES, INC.
Chatham, NJ 07928
TOSYMRA is a registered trademark of Tonix Medicines, Inc.
This product may be covered by one or more U.S. patent(s).

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

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