

## 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<sub>1B/1D</sub>) 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 may be 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<sub>1</sub> agonist (e.g., another triptan) or of an ergotamine-containing medication (4)
- Concurrent or recent (past 2 weeks) use of monoamine oxidase-A inhibitors (4)

- Hypersensitivity to sumatriptan (angioedema and anaphylaxis seen) (4)
  - Severe hepatic impairment (4)
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- 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 Upsher-Smith Laboratories, LLC at 1-855-899-9180 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.**

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## 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 1/4 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-hydroxytryptamine (5-HT<sub>1</sub>) 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<sub>1</sub> 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-naïve 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<sub>1</sub> 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<sub>1</sub> agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT<sub>1</sub> agonists has 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<sub>1</sub> 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

Table continued at top of next column

Adverse Reaction	Percent of Subjects Reporting	
	Sumatriptan Injection 6 mg Subcutaneous (n = 547)	Placebo (n = 370)
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	5	<1
Pressure in chest	3	<1
Ear, nose, and throat		
Throat discomfort	3	<1
Discomfort: nasal cavity/sinuses	2	<1
Injection site reaction <sup>a</sup>	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

<sup>a</sup> 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 ZEMBRACE 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<sub>1</sub> Agonists

Because their vasospastic effects may be additive, coadministration of ZEMBRACE SymTouch injection and other 5-HT<sub>1</sub> 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 preclampsia 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 defining 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 (cardiothoracic 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 cardiovascular 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 dosage 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 were expected from animal data, doses at 0.1 g/kg, rats at 2 g/kg) to possibly cause convulsions, tremor, inactivity, erythema of the extremities, reduced



## 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.upsher-smith.com](http://www.upsher-smith.com) or call 1-888-650-3789.

## What are the ingredients in ZEMBRACE SymTouch Injection?

Active ingredient: sumatriptan succinate

Inactive ingredients: sodium chloride, water for injection

Manufactured for  
**UPSHER-SMITH LABORATORIES, LLC**  
Maple Grove, MN 55369

ZEMBRACE and SymTouch are registered trademarks of Upsher-Smith Laboratories, LLC.

This product may be covered by one or more U.S. patent(s). See [www.uspatents.com](http://www.uspatents.com).

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

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**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<sub>max</sub> of subcutaneous sumatriptan were similar in black (n = 34) and Caucasian (n = 38) healthy male subjects.

**Drug Interaction Studies:**

**Monamine 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<sup>2</sup> 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 <sup>a</sup>				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

<sup>a</sup> 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 <sup>a</sup> (n = 190)	Sumatriptan 6 mg (n = 384)	Placebo <sup>a</sup> (n = 180)	Sumatriptan 6 mg <sup>d</sup> (n = 350)
Subjects with pain relief (grade 0/1)	18%	70% <sup>a</sup>	26%	70% <sup>a</sup>
Subjects with no pain	5%	48% <sup>a</sup>	13%	49% <sup>a</sup>
Subjects without nausea	48%	73% <sup>a</sup>	50%	73% <sup>a</sup>
Subjects without photophobia	23%	56% <sup>a</sup>	25%	58% <sup>a</sup>
Subjects with little or no clinical disability <sup>b</sup>	34%	76% <sup>a</sup>	34%	76% <sup>a</sup>

  

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

<sup>a</sup> P<0.05 versus placebo.

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

<sup>c</sup> Includes patients that may have received an additional placebo injection 1 hour after the initial injection.

<sup>d</sup> 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<sup>®</sup> SymTouch<sup>®</sup> 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 pre-filled, ready-to-use, single dose, disposable auto-injector unit (NDC # 0245-0809-89).

- Each carton contains 4 units (NDC # 0245-0809-38) 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 methysergide) is contraindicated [see *Contraindications* (4), *Drug Interactions* (7.1, 7.3)].

### Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with the use of 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

**UPSHER-SMITH LABORATORIES, LLC**  
Maple Grove, MN 55369

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