

Get migraine pain relief–fast^{1,2}

Zembrace[®] SymTouch[®] is a prescription medicine used to treat acute migraine headaches with or without aura in adults 18 years of age and older who have been diagnosed with migraine.

Zembrace[®] SymTouch[®] is not used to prevent or decrease the number of migraines you have.

Do not take Zembrace^{*} SymTouch^{*} if you have hemiplegic migraines or basilar migraines. This is not the only reason not to take Zembrace^{*} SymTouch^{*}. If you are not sure if you have these types of migraines, ask your healthcare provider.



Migraine is a neurological condition

A migraine can cause severe pain, pulsing or throbbing in the head that can last from a few hours to a few days if untreated. This–in addition to symptoms other than pain–makes migraine distinct from just a bad headache:

- Migraines can occur with varying frequency-from only rarely to many days each month. For some people, the symptoms can be so disabling that it disrupts their personal, family and work life.
- Migraine symptoms vary from person to person and can include intense pain; pain on one side of the head; nausea or vomiting; extreme sensitivity to light, noise or smells; blurred vision and dizziness. Some patients may experience an "aura" before migraine.

Zembrace'SYMTOUCH' (sumatriptan injection) 3 mg

What is Zembrace[®] SymTouch[®]

Zembrace[®] SymTouch[®] is a prescription medicine used to treat acute migraine headaches with or without aura in adults 18 years of age and older who have been diagnosed with migraine.

How can Zembrace[®] SymTouch[®] help

Zembrace^{*} SymTouch^{*} is a ready-touse, single-use pen (auto-injector) containing 3 mg of sumatriptan. 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.

Do not use Zembrace^{*} SymTouch^{*} if you have: heart problems or a history of heart problems; had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation. These are not all of the reasons you should not use Zembrace^{*} SymTouch^{*}.



When timing is everything

You want migraine pain relief–fast.^{1,2} Zembrace[®] SymTouch[®] may help you return to the moments that matter most.



If you suffer from any of the following migraines, Zembrace[®] SymTouch[®] may be able to help:



Morning migraine Nearly half of all migraine attacks occur between 4 and 9 a.m.³



Rapid-onset migraine A migraine that reaches full force quickly.



Migraine with nausea

73% of patients with migraine have experienced nausea (with or without vomiting) during migraine attacks.⁴

Zembrace^{*} SymTouch^{*} is indicated for the acute treatment of migraine with or without aura in adults.





In as little as 10 minutes, you may get migraine pain relief (17% of patients for sumatriptan 3 mg vs. 5% for placebo).⁺ One study showed that 60% of people experienced pain relief within 2 hours of use (vs. 21% for placebo).¹

†Time to onset and degree of pain relief varies by patient.

The most common side effects of Zembrace*

SymTouch* include pain and 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.

Simple to use

Zembrace[®] SymTouch[®] is a convenient, ready-to-use pen:

- Smallest needle in a sumatriptan pen⁵
- Simple two-step injection process^{1,6}
- Do not refrigerate[‡]

\$Store between 68°F and 77°F. Excursions permitted between 59°F and 86°F.



Two-step injection process

Remove protective cap.

Zembraceswinouch tempraceswinouch texestomeres and texture

X Only

Before administering, be sure that the injection site is properly cleaned. Ensure that the used pen is properly disposed of immediately after use.



See accompanying full Instructions for Use.



Push against clean injection site and hold until you hear the device click.



Wait 5 seconds after second click before removing.



ACCESS PATHWAYS® PROGRAM

How to save on Zembrace[®] SymTouch[®]

The Access Pathways[®] Program is a dedicated savings and support program to help you access Zembrace[®] SymTouch[®] for as little as \$0.*

Access Pathways^{*}, in partnership with BlinkRx, offers:



Eligible, commercially ensured patients may pay as little as \$0* per prescription, per month.







Dedicated customer support to guide you through the process.



*Restrictions and quantity limits apply. Visit <u>Zembrace.com</u> to view complete program terms and conditions. Medicare, Medicaid, and other federal and state healthcare program patients are not eligible.

IMPORTANT SAFETY INFORMATION

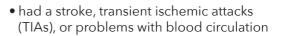
Zembrace SymTouch (Zembrace) can cause serious side effects, including heart attack and other heart problems, which may lead to death. Stop use and get emergency help if you have any signs of a heart attack:

- discomfort in the center of your chest that lasts for more than a few minutes or 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 is not for people with risk factors for heart disease (high blood pressure or cholesterol, smoking, overweight, diabetes, family history of heart disease) unless a heart exam shows no problem.

Do not use Zembrace if you have:

- history of heart problems
- narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular disease)
- uncontrolled high blood pressure
- hemiplegic or basilar migraines. If you are not sure if you have these, ask your provider.



Zembrace[®]SYMTOUCH[®] (sumatriptan injection) 3 mg

- severe liver problems
- taken any of the following medicines in the last 24 hours: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, ergotamines, dihydroergotamine.
- 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 provider for a list of these medicines if you are not sure.
- an allergy to sumatriptan or any of the components of Zembrace

Tell your provider about all of your medical conditions and medicines you take, including vitamins and supplements.

Zembrace can cause dizziness, weakness, or drowsiness. If so, do not drive a car, use machinery, or do anything where you need to be alert.

Zembrace may cause serious side effects including:

- changes in color or sensation in your fingers and toes
- sudden or severe stomach pain, stomach pain after meals, weight loss, nausea or vomiting, constipation or diarrhea, bloody diarrhea, fever

Important Safety Information continued on next page.



- 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 one or both legs or feet
- increased blood pressure including a sudden severe increase even if you have no history of high blood pressure
- medication overuse headaches from using migraine medicine for 10 or more days each month. If your headaches get worse, call your provider.
- serotonin syndrome, a rare but serious problem that can happen in people using Zembrace, especially when used with anti-depressant medicines called SSRIs or SNRIs. Call your provider right away if you have: 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; or trouble walking.
- hives (itchy bumps); swelling of your tongue, mouth, or throat
- seizures even in people who have never had seizures before

The most common side effects of Zembrace include: pain and redness at 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 provider if you have any side effect that bothers you or does not go away. These are not all the possible side effects of Zembrace. For more information, ask your provider.

This is the most important information to know about Zembrace but is not comprehensive. For more information, talk to your provider and read the <u>Patient</u> <u>Information</u> and <u>Instructions for Use</u>. You can also visit <u>www.tonixpharma.com</u> or call 1-888-650-3789.

You are encouraged to report adverse effects of prescription drugs to the FDA. Visit <u>www.fda.gov/medwatch</u>, or call 1-800-FDA-1088.

INDICATION AND USAGE

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

Zembrace is not used to prevent migraines. It is not known if it is safe and effective in children under 18 years of age.



Learn more about Zembrace[®] SymTouch[®] at <u>Zembrace.com</u>

References

- 1. Zembrace SymTouch [package insert]. Catham, NJ: Tonix Medicines, Inc.: February 2021.
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- 3. Top 10 migraine triggers and how to deal with them. American Migraine Foundation. <u>https://americanmigrainefoundation.org/</u> <u>resource-library/top-10-migraine-triggers-and-how-to-deal-with-</u> <u>them/</u>. Published July 27, 2017. Accessed 2021.
- Newman LC. Why triptan treatment can fail: focus on gastrointestinal manifestations of migraine. *Headache*. 2013;53 Suppl 1:11-16.
- 5. Data on file. Catham, NJ: Tonix Medicines, Inc.: 2021.
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HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use ZEMBRACE® SymTouch® safely and See full prescribing in 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 cardiad 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-HT₁ 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)

FULL PRESCRIBING INFORMATION: CONTENTS* INDICATIONS AND USAGE

- DOSAGE AND ADMINISTRATION
- 2.1 Dosing Information2.2 Administration Using ZEMBRACE SymTouch
- DOSAGE FORMS AND STRENGTHS

CONTRAINDICATIONS

WARNINGS AND PRECAUTIONS

- 5.1 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina
- Arrhythmias Chest, Throat, Neck, and/or Jaw Pain/Tightness/ 5.3
- Pressure
- Cerebrovascular Events Other Vasospasm Reactions
- 5.6 Medication Overuse Headache
- Serotonin Syndro Increase in Blood Pressure
- 5.9 Hypersensitivity Reactions
- 5.10 Seizures ADVERSE REACTIONS Clinical Trials Experience 6.2 Post-marketing Experience
- DRUG INTERACTIONS

Ergot-Containing Drugs Monoamine Oxidase-A Inhibitors 7.2

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAG

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 ent 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 1/2 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-injecto

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-HT₁) 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)].

•	Hypersensitivity to sumatriptan (angioedema and
	anaphylaxis seen) (4)
٠	Severe hepatic impairment (4)

--- WARNINGS AND PRECAUTIONS Myocardial ischemia/infarction and Prinzmetal's angina: Perform cardiac evaluation in patients with multiple

Arrhythmias: Discontinue ZEMBRACE SymTouch it

heaviness: Generally, not associated with myocardial

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Discontinue ZEMBRACE SymTouch if occurs.

Gastrointestinal ischemia and reactions, peripheral vasospastic reactions: Discontinue ZEMBRACE

SymTouch if occurs. (5.5) • Medication overuse headache: Detoxification may be

Serotonin syndrome: Discontinue ZEMBRACE SymTouc

Seizures: Use with caution in patients with epilepsy or a

---- ADVERSE REACTIONS

Most common adverse reactions (\geq 5% and > placebo)

To report SUSPECTED ADVERSE REACTIONS, contact

Upsher-Smith Laboratories, LLC at 1-855-899-9180 or

-- USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm

7.4 Selective Serotonin Reuptake Inhibitors/Serotoni

Norepinephrine Reuptake Inhibitors and Serotonir

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility 13.2 Animal Toxicology and/or Pharmacology

*Sections or subsections omitted from the full prescribing

Revised 2/2021

See 17 for PATIENT COUNSELING INFORMATION and

FDA-approved patient labeling

7.3 Other 5-HT1 Agonists

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12.1 Mechanism of Action 12.2 Pharmacodynamics

10 OVERDOSAGE

11 DESCRIPTION

8.2 Lactation

FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

were injection site reactions, tingling, dizziness/ve warm/hot sensation, burning sensation, feeling of

heaviness, pressure sensation, flushing, feeling of tightness, and numbness/paresthesia. (6.1)

ischemia; evaluate for coronary artery disease in patients

Chest/throat/neck/iaw pain, tightness, pressure, or

cardiovascular risk factors. (5.1)

occurs. (5.2)

at high risk. (5.3)

necessary. (5.6)

f occurs. (5.7)

lowered seizure threshold. (5.10)

(5.4)

	Subcutaneous (n = 547)	(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	3	<1
Pressure in chest	2	<1
Ear, nose, and throat		
Throat discomfort	3	<1
Discomfort: nasal cavity/sinuses	2	<1
Injection site reaction ^a	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

Percent of Subjects Reporting

Placebo

Sumatriptan Injection 6 mg

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, palpitation Neurological Dystonia, tremo

Adverse Reactio

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-HT₁ Agonists

Because their vasospastic effects may be additive, coadministration of ZEMBRACE SymTouch injection and other 5-HT₁ 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.

<u>Data</u> 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 na a coop dang data non ne orecash moleae brinn register, ne o intra commar with report on a grant of the orecash moleae brinn register, new of the original to mole of the commar with report of the original first trimester exposure to sumarity fan, 107 infants were born with malformations (relative risk 0.99 [95% Cl: 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 intravenous no-effect doses for developmental toxicity in rabbits were 15 and 0.75 mg/kg/day, respectively.

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

have high blood pressure

have high cholesterol levels

· have a family history of heart disease

What is ZEMBRACE SymTouch?

diagnosed with migraine.

migraines you have.

under 18 years of age.

blood circulation

almotriptan

frovatriptan

naratriptan

rizatriptan

ergotamines

dihydroergotamine

ZEMBRACE SymTouch?

eletriptan

severe liver problems

ZEMBRACE SymTouch.

- nausea or vomiting
- · feeling lightheaded

are overweight

have diabetes

smoke

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:

ZEMBRACE SymTouch is a prescription medicine used to treat acute

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

ZEMBRACE SymTouch is not used to prevent or decrease the number of

It is not known if ZEMBRACE SymTouch is safe and effective in children

narrowing of blood vessels to your legs, arms, stomach, or kidney

hemiplegic migraines or basilar migraines. If you are not sure if you

had a stroke, transient ischemic attacks (TIAs), or problems with your

SymTouch. See the end of this leaflet for a complete list of ingredients in

have these types of migraines, ask your healthcare provider.

• an allergy to sumatriptan or any of the ingredients in ZEMBRACE

taken any of the following medicines in the last 24 hours:

migraine headaches with or without aura in adults who have been

basilar (rare form of migraine with aura) migraines.

Who should not take ZEMBRACE SymTouch?

Do not take ZEMBRACE SymTouch if you have:

heart problems or a history of heart problems

(peripheral vascular disease)

uncontrolled high blood pressure

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-HT₁ 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-HT₁ 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-HT1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT₁ agonist having been administered in the increases in a home of cases, it appears possible unit the coronvascular events were primary, the of the agoinst name of 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 Vasosnasm Reactions

ZEMBRACE SymTouch injection may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infraction (presenting with abdominal plana of bloody diarrhab, splenic infraction, and Raynaud's syndrome. In patients who experience symptoms or signs suggestive of non-coronary vasospasm reaction following the use of any 5-HT₁ 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-HT₁ agonists Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT₁ agonists have not been clearly established.

5.6 Medication Overuse Headach

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 necess

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., hypertelfexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually occurs ms usually occurs withi minutes to hours of receiving a new or a greater dose of a serotonergic medication. Discontinue ZEMBRACE SymTouch injection it 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-HT₁ 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

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)

Percent of Subjects F	Percent of Subjects Reporting		
Sumatriptan Injection 6 mg Subcutaneous (n = 547)	Placebo (n = 370)		
42	9		
14	3		
11	4		
7	<1		
	Sumatriptan Injection 6 mg Subcutaneous (n = 547) 42		

Table continued at top of next colum

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 conditio **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 n 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 summarity. 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, does 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

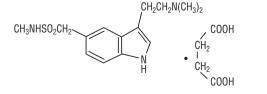
Coronary vasospasm was observed after intravenous administration of sumatriptan injection [see Contraindications (4)]. Overdoses would be expected from animal data (dogs at 0.1 g/kg, rats at 2 g/kg) to possibly cause convulsions, tremor, inactivity, erythema of the extremities, reduced respiratory rate, 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_{IB/ID} 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 $C_{ta}H_{21}N_{3}O_{2}Sc_{4}H_{6}O_{4}$, 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 SvmTouch 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, USF

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) rial 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: After a single of ing solucitations into an electron into the denoise at a first and in the location into the single of the solution T_0 kg), the maximum secure concentration (T_{max}) of smartpitch mass (mean \pm 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 Cmax of 61 ± 15 ng/mL by manual injection versus 52 ±15 ng/mL by auto-injector techniques. The Tmax or amount absorbed was not significantly altered by either the site or technique of injectior

Distribution: Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL, is low annroximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated and the state of the s

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. Nost of a radiolabeled dose of sumatriptan excreted in the urine is the major metabolite indole acetic acid (IAA) or the IAA glucur both of which are inactive

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

What should I tell my healthcare provider before taking

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

- have high blood pressure
- have high cholesterol
- have diabetes
- smoke

above.

- 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

Ask your healthcare provider or pharmacist for a list of these medicines if

Know the medicines you take. Keep a list of them to show your healthcare

• Certain people should take their first dose of ZEMBRACE SymTouch in

their healthcare provider's office or in another medical setting. Ask your

• Use ZEMBRACE SymTouch exactly as your healthcare provider tells you

Your healthcare provider may change your dose. Do not change your

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

If you did not get any relief after the first injection, do not give a second

start, but it may be given at any time during a migraine headache attack.

You may use a second dose of ZEMBRACE SymTouch after the first dose

medication separated by at least 1 hour, but not sooner, if your headache

of ZEMBRACE SymTouch OR after one dose of another sumatriptan

Do not take more than a total of 12 mg of ZEMBRACE SymTouch in a

SymTouch you can take in a 24-hour period if you take another form of

If you use too much ZEMBRACE SymTouch, call your healthcare provider

You should write down when you have headaches and when you take

ZEMBRACE SymTouch so you can talk with your healthcare provider

ZEMBRACE SymTouch can cause dizziness, weakness, or drowsiness. If

comes back or you only get some relief after your first injection.

24-hour period. Talk to your doctor about how many ZEMBRACE

sumatriptan medication in between ZEMBRACE SymTouch.

or go to the nearest hospital emergency room right away.

about how ZEMBRACE SymTouch is working for you.

anything where you need to be alert.

What should I avoid while taking ZEMBRACE SymTouch?

you have these symptoms, do not drive a car, use machinery, or do

dose without first talking with your healthcare provider.

injection without first talking with your healthcare provider.

healthcare provider if you should take your first dose in a medical setting.

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)

provider or pharmacist when you get a new medicine.

How should I take ZEMBRACE SymTouch?

tricyclic antidepressants (TCAs)

you are not sure.

to use it.

monoamine oxidase inhibitors (MAOIs)

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

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 sumatrintan was 1 194 + 149 mL/min and the terminal half-life was 115 \pm 19 minutes

Specific Populations:

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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 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 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 subiects

Drug Interaction Studies

Monoamine Oxidase-A Inhibitors: In a trial of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of sumatripitan, resulting in a 2-fold increase in the area under the sumatripitan 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/m² basis. There was no evidence in either species of an increase in tumors related to sumatriptan administration.

<u>Mutagenesis</u>

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

Dose of		Percent Patients With Reliefa			
Sumatriptan Injection	at 10 Minutes	at 30 Minutes	at 1 Hour	at 2 Hours	Incidence (%)
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

^a 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 pair (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 Symp	ptoms After 1 and 2 Hours of Treatment in Studies 2 and 3 $% \left({{\left[{{\left[{{\left[{\left[{\left[{\left[{\left[{\left[{\left[$
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1-Hour Data	Study 2		Study 3	
	Placebo (n = 190)	Sumatriptan 6 mg (n = 384)	Placebo (n = 180)	Sumatriptan 6 m (n = 350)
Subjects with pain relief (grade 0/1)	18%	70%a	26%	70% ^a
Subjects with no pain	5%	48%ª	13%	49% ^a
Subjects without nausea	48%	73%a	50%	73% ^a
Subjects without photophobia	23%	56%a	25%	58% ^a
Subjects with little or no clinical disability ^b	34%	76%ª	34%	76%ª
2-Hour Data	Study 2		Study 3	
	Placeboc	Sumatriptan 6 mg ^d	Placeboc	Sumatriptan 6 m
Subjects with pain relief (grade 0/1)	31%	81% ^a	39%	82% ^a
Subjects with no pain	11%	63%ª	19%	65% ^a
Subjects without nausea	56%	82%a	63%	81% ^a
Subjects without photophobia	31%	72%ª	35%	71% ^a
Subjects with little or no clinical disability ^b	42%	85%ª	49%	84%a

function normally

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

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

The efficacy of sumatriptan 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%

condition for which it was not prescribed. Do not give ZEMBRACE	16 HOW SUPPLIED/STORAGE AND HANDLING
SymTouch to other people, even if they have the same symptoms you have. It may harm them.	 16.1 How Supplied • ZEMBRACE® SymTouch® 3 mg/0.5 mL Injection contains sumatriptan as the succinate salt and is supplied as a clear, coloriess to pale yellow, sterile, nonpyrogenic solution in a prefilied, ready-to-use, single dose, disposable auto-injector unit (NDC # 0245-0809-89).
This Patient Information leaflet summarizes the most important	• Each carton contains 4 units (NDC # 0245-0809-38) and a Patient Information and Instructions for Use leaflet.
information about ZEMBRACE SymTouch. If you would like more information, talk with your healthcare provider. You can ask your	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.
healthcare provider or pharmacist for information about ZEMBRACE	17 PATIENT COUNSELING INFORMATION
	Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
SymTouch that is written for healthcare professionals.	Risk of Myocardial Ischemia and/or Infarction, Prinzmetal's Angina. Other Vasospasm-Related Events, Arrhythmias, and Cerebrovascular Events
For more information, go to www.upsher-smith.com or call 1-888-650-3789.	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 <i>[see Warnings and Precautions (5.1, 5.2, 5.4, 5.5, 5.8].</i>
What are the ingredients in ZEMBRACE SymTouch Injection?	Hypersensitivity Reactions
Active ingredient: sumatriptan succinate	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)].
Inactive ingredients: sodium chloride, water for injection	Concomitant Use with Other Triptans or Ergot Medications
Manufactured for	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)].
UPSHER-SMITH LABORATORIES, LLC	Serotonin Syndrome
Maple Grove, MN 55369	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 <i>(see Warnings and Precautions (5.7), Drug Interactions (7.4)</i>].
	Medication Overuse Headache
ZEMBRACE and SymTouch are registered trademarks of Upsher-Smith	Inform patients that use of acute migraine drugs for 10 or more days per month may lead to an exacerbation of headache and
Laboratories, LLC.	encourage patients to record headache frequency and drug use (e.g., by keeping a headache diary) [see Warnings and Precautions (5.6)].
This product may be covered by one or more U.S. patent(s). See	Pregnancy
	Advise patients to notify their healthcare provider if they become pregnant during treatment or plan to become pregnant <i>[see Use in Specific Populations (8.1)]</i> .
www.uslpatents.com.	Lactation
This Patient Information has been approved by the U.S. Food and Drug	Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed [see Use in Specific Populations (8.2)].
Administration.	Ability to Perform Complex Tasks
Autonisti ation.	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.
TS-276-US Revised: 2/2	
	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 1/4 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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This product may be covered by one or more U.S. patent(s). See www.uslpatents.com.

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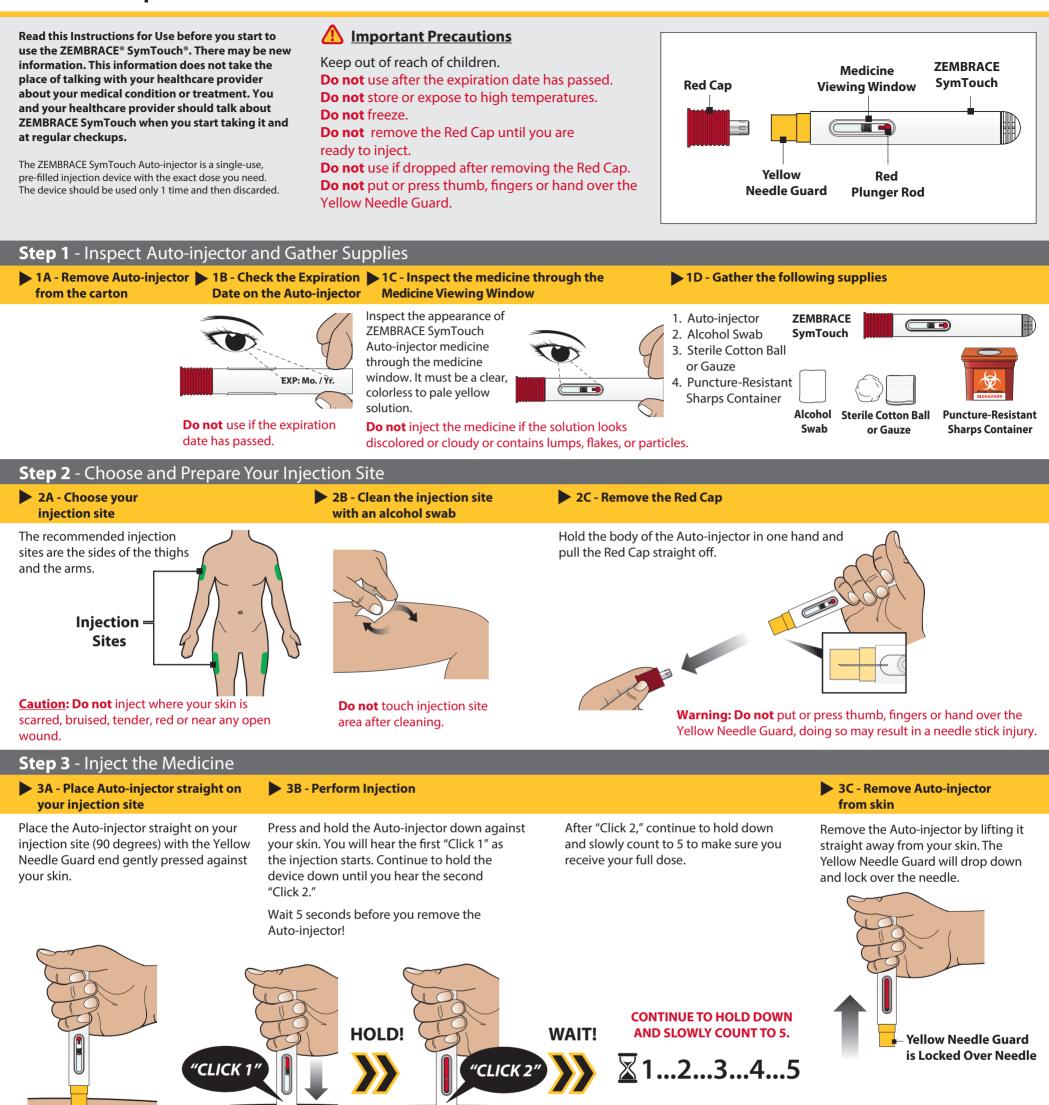
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Revised: 2/2021



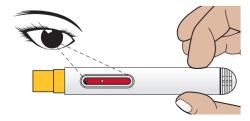
<u>Important</u>: To receive your full dose, always hold the Auto-injector down on your injection site for additional time after you hear the second click. This allows all of the medicine to be delivered.

Step 4 - Confirm Injection and Dispose the Auto-injector

4A - Confirm Red Color in Medicine Viewing Window

4B - Disposal of the Auto-injector

Look to confirm that the Red Plunger Rod has filled the Medicine Viewing Window. This means you received the full dose.



Caution: Call your healthcare provider if the Red Plunger Rod has not filled the Medicine Viewing Window. This may mean that only a partial dose was delivered.

Do not try to reuse the Auto-injector.

Put your used Auto-injector, caps, needles, and sharps in an FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and syringes in your household trash. Do not recycle your used sharps disposal container.

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is: made of a heavy-duty plastic; can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out; upright and stable during use; leak-resistant; and properly labeled to warn of hazardous waste inside the container. When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

If needed, make sure you get a refill of your Auto-injector.

BIOHAZARD

4C - Treat Injection Site

Treat the injection site with a cotton ball, gauze pad or bandage, as needed.

Do not rub the injection site.

Manufactured for **Tonix Medicines, Inc.** Chatham, NJ 07928

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

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

TS-275-US

Revised: 12/2023

PM-000369.01