HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IMITREX safely and effectively. See full prescribing information for IMITREX.

IMITREX (sumatriptan succinate) Tablets, for oral use
Initial U.S. Approval: 1992

----------INDICATIONS AND USAGE----------

IMITREX 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 headache has been established. (1)
- Not indicated for the prophylactic therapy of migraine attacks. (1)
- Not indicated for the treatment of cluster headache. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Single dose of 25- mg, 50-mg, or 100-mg tablet.(2.1)
- A second dose should only be considered if some response to the first dose was observed. Separate doses by at least 2 hours. (2.1)
- Maximum dose in a 24-hour period: 200 mg. (2.1)
- Maximum single dose should not exceed 50 mg in patients with mild to moderate hepatic impairment. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 25 mg, 50 mg, and 100 mg (3)

----------CONTRAINDICATIONS----------

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

---------- WARNINGS AND PRECAUTIONS ----------

- Myocardial ischemia/infarction and Prinzmetal's angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors. (5.1)
- Arrhythmias: Discontinue IMITREX 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 IMITREX if occurs. (5.4)
- Gastrointestinal ischemic reactions and peripheral vasospastic reactions: Discontinue IMITREX if occurs. (5.5)
- Medication overuse headache: Detoxification may be necessary. (5.6)
- Serotonin syndrome: Discontinue IMITREX 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 (≥2% and >placebo) were paresthesia, warm/cold sensation, chest pain/tightness/pressure and/or heaviness, neck/throat/jaw pain/tightness/pressure, other sensations of pain/pressure/tightness/heaviness, vertigo, and malaise/fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

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

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

Revised: XX/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IMITREX® Tablets are indicated for the acute treatment of migraine with or without aura in adults.

Limitations of Use:

- Use only if a clear diagnosis of migraine headache has been established. If a patient has no response to the first migraine attack treated with IMITREX, reconsider the diagnosis of migraine before IMITREX is administered to treat any subsequent attacks.
- IMITREX is not indicated for the prevention of migraine attacks.
- Safety and effectiveness of IMITREX Tablets have not been established for cluster headache.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of IMITREX Tablets is 25 mg, 50 mg, or 100 mg. Doses of 50 mg and 100 mg may provide a greater effect than the 25-mg dose, but doses of 100 mg may not provide a greater effect than the 50-mg dose. Higher doses may have a greater risk of adverse reactions *[see Clinical Studies (14)]*.

If the migraine has not resolved by 2 hours after taking IMITREX Tablets, or returns after a transient improvement, a second dose may be administered at least 2 hours after the first dose. The maximum daily dose is 200 mg in a 24-hour period.

Use after IMITREX Injection**:** If the migraine returns following an initial treatment with IMITREX (sumatriptan succinate) Injection, additional single IMITREX Tablets (up to 100 mg/day) may be given with an interval of at least 2 hours between tablet doses.

The safety of treating an average of more than 4 headaches in a 30-day period has not been established.

2.2 Dosing in Patients With Hepatic Impairment

If treatment is deemed advisable in the presence of mild to moderate hepatic impairment, the maximum single dose should not exceed 50 mg *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

25 mg Tablets: White, triangular-shaped, film-coated, and debossed with “I” on one side and “25” on the other.

50 mg Tablets: White, triangular-shaped, film-coated, and debossed with “IMITREX 50” on one side and a chevron shape (^) on the other.

100 mg Tablets: Pink, triangular-shaped, film-coated, and debossed with "IMITREX 100" on one side and a chevron shape (^) on the other.

4 CONTRAINDICATIONS

IMITREX Tablets are contraindicated in patients with:

- Ischemic coronary artery disease (CAD) (angina pectoris, history of myocardial infarction, or documented silent ischemia) or coronary artery vasospasm, including Prinzmetal's angina *[see Warnings and Precautions (5.1)]*
- Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders *[see Warnings and Precautions (5.2)]*
- History of stroke or transient ischemic attack (TIA) or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke *[see Warnings and Precautions (5.4)]*
- Peripheral vascular disease *[see Warnings and Precautions (5.5)]*
- Ischemic bowel disease *[see Warnings and Precautions (5.5)]*
- Uncontrolled hypertension *[see Warnings and Precautions (5.8)]*
- Recent use (i.e., within 24 hours) of ergotamine-containing medication, ergot-type medication (such as dihydroergotamine or methysergide), or another 5-hydroxytryptamine$_1$ (5-HT$_1$) agonist *[see Drug Interactions (7.1, 7.3)]*
- Concurrent administration of a monoamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*
- Hypersensitivity to IMITREX (angioedema and anaphylaxis seen) *[see Warnings and Precautions (5.9)]*
- Severe hepatic impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*

5 WARNINGS AND PRECAUTIONS

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

The use of IMITREX Tablets 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 IMITREX Tablets. Some of these reactions occurred in patients without known CAD. IMITREX Tablets 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 IMITREX Tablets. If there is evidence of CAD or

coronary artery vasospasm, IMITREX Tablets are contraindicated. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first dose of IMITREX Tablets in a medically supervised setting and performing an electrocardiogram (ECG) immediately following administration of IMITREX Tablets. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of IMITREX Tablets.

5.2 Arrhythmias

Life-threatening disturbances of cardiac rhythm, including ventricular tachycardia and ventricular fibrillation leading to death, have been reported within a few hours following the administration of 5-HT_1 agonists. Discontinue IMITREX Tablets if these disturbances occur. IMITREX Tablets are 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 IMITREX Tablets and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. The use of IMITREX Tablets is contraindicated in patients with CAD and those with Prinzmetal's variant angina.

5.4 Cerebrovascular Events

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

Before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, exclude other potentially serious neurological conditions. IMITREX Tablets are contraindicated in patients with a history of stroke or TIA.

5.5 Other Vasospasm Reactions

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

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

5.6 Medication Overuse Headache

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

5.7 Serotonin Syndrome

Serotonin syndrome may occur with IMITREX Tablets, 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 IMITREX Tablets if serotonin syndrome is suspected.

5.8 Increase in Blood Pressure

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

5.9 Anaphylactic/Anaphylactoid Reactions

Anaphylactic/anaphylactoid reactions have occurred in patients receiving IMITREX. 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. IMITREX Tablets are contraindicated in patients with a history of hypersensitivity reaction to IMITREX.

5.10 Seizures

Seizures have been reported following administration of IMITREX. 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. IMITREX

Tablets 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 adverse reactions are discussed in more detail in other sections of the prescribing information:

- 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) and 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.

Table 1 lists adverse reactions that occurred in placebo-controlled clinical trials in patients who took at least 1 dose of study drug. Only treatment-emergent adverse reactions that occurred at a frequency of 2% or more in any group treated with IMITREX Tablets and that occurred at a frequency greater than the placebo group are included in Table 1.

Table 1. Adverse Reactions Reported by at Least 2% of Patients Treated With IMITREX Tablets and at a Greater Frequency Than Placebo

Adverse Reaction	Percent of Patients Reporting			
	IMITREX Tablets 25 mg (n = 417)	IMITREX Tablets 50 mg (n = 771)	IMITREX Tablets 100 mg (n = 437)	Placebo (n = 309)
Atypical sensations	5	6	6	4
Paresthesia (all types)	3	5	3	2
Sensation warm/cold	3	2	3	2
Pain and other pressure sensations	6	6	8	4
Chest - pain/tightness/ pressure and/or heaviness	1	2	2	1
Neck/throat/jaw - pain/ tightness/pressure	<1	2	3	<1
Pain - location specified	2	1	1	1
Other - pressure/tightness/ heaviness	1	1	3	2
Neurological				
Vertigo	<1	<1	2	<1
Other				
Malaise/fatigue	2	2	3	<1

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of IMITREX Tablets, IMITREX Nasal Spray, and IMITREX 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. These reactions have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to IMITREX or a combination of these factors.

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 IMITREX Tablets within 24 hours of each other is contraindicated.

7.2 Monoamine Oxidase-A Inhibitors

MAO-A inhibitors increase systemic exposure by 7-fold. Therefore, the use of IMITREX Tablets in patients receiving MAO-A inhibitors is contraindicated *[see Clinical Pharmacology (12.3)]*.

7.3 Other 5-HT_1 Agonists

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled trials in pregnant women. In developmental toxicity studies in rats and rabbits, oral administration of sumatriptan to pregnant animals was associated with embryolethality, fetal abnormalities, and pup mortality. When administered by the intravenous route to pregnant rabbits, sumatriptan was embryolethal. IMITREX Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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, or approximately 3 times the maximum recommended human dose (MRHD) of 200 mg/day on a mg/m^2 basis. Oral administration of sumatriptan to pregnant rabbits during the period of organogenesis resulted in increased incidences of embryolethality and fetal cervicothoracic vascular and skeletal abnormalities. Intravenous administration of sumatriptan to pregnant rabbits during the period of organogenesis resulted in an increased incidence of embryolethality. The highest oral and intravenous no-effect doses for developmental toxicity in rabbits were 15 (approximately 2 times the MRHD on a mg/m^2 basis) 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, or approximately 2 times the MRHD on a mg/m^2 basis. 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, or approximately 3 times the MRHD on a mg/m^2 basis. 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, or approximately 5 times the MRHD on a mg/m^2 basis.

8.3 Nursing Mothers

Sumatriptan is excreted in human milk following subcutaneous administration. Infant exposure to sumatriptan can be minimized by avoiding breastfeeding for 12 hours after treatment with IMITREX Tablets.

8.4 Pediatric Use

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

Two controlled clinical trials evaluated IMITREX Nasal Spray (5 to 20 mg) in 1,248 adolescent migraineurs aged 12 to 17 years who treated a single attack. The trials did not establish the efficacy of IMITREX Nasal Spray compared with placebo in the treatment of migraine in adolescents. 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 IMITREX (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These trials did not establish the efficacy of oral IMITREX compared with placebo in the treatment of migraine in adolescents. 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 adolescents.

Postmarketing experience documents that serious adverse reactions have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal IMITREX. 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 IMITREX; 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 IMITREX are not presently available.

8.5 Geriatric Use

Clinical trials of IMITREX Tablets did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

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

8.6 Hepatic Impairment

The maximum single dose in patients with mild to moderate hepatic impairment should not exceed 50 mg. IMITREX Tablets are contraindicated in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Patients in clinical trials (N = 670) received single oral doses of 140 to 300 mg without significant adverse reactions. Volunteers (N = 174) received single oral doses of 140 to 400 mg without serious adverse reactions.

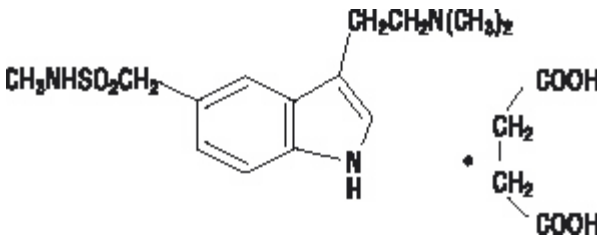
Overdose in animals has been fatal and has been heralded by convulsions, tremor, paralysis, inactivity, ptosis, erythema of the extremities, abnormal respiration, cyanosis, ataxia, mydriasis, salivation, and lacrimation.

The elimination half-life of sumatriptan is approximately 2.5 hours *[see Clinical Pharmacology (12.3)]*, and therefore monitoring of patients after overdose with IMITREX Tablets should continue for at least 12 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

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



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

Each IMITREX Tablet for oral administration contains 35, 70, or 140 mg of sumatriptan succinate equivalent to 25, 50, or 100 mg of sumatriptan, respectively. Each tablet also contains the inactive ingredients croscarmellose sodium, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, and sodium bicarbonate. Each 100-mg tablet also contains hypromellose, iron oxide, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

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

Heart Rate: Transient increases in blood pressure observed in some patients 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

Absorption and Bioavailability: The mean maximum concentration following oral dosing with 25 mg is 18 ng/mL (range: 7 to 47 ng/mL) and 51 ng/mL (range: 28 to 100 ng/mL) following oral dosing with 100 mg of sumatriptan. This compares with a C_{max} of 5 and 16 ng/mL following dosing with a 5- and 20-mg intranasal dose, respectively. The mean C_{max} following a 6-mg subcutaneous injection is 71 ng/mL (range: 49 to 110 ng/mL). The bioavailability is approximately 15%, primarily due to presystemic metabolism and partly due to incomplete absorption. The C_{max} is similar during a migraine attack and during a migraine-free period, but the T_{max} is slightly later during the attack, approximately 2.5 hours compared with 2.0 hours. When given as a single dose, sumatriptan displays dose proportionality in its extent of absorption

(area under the curve [AUC]) over the dose range of 25 to 200 mg, but the C_{max} after 100 mg is approximately 25% less than expected (based on the 25-mg dose).

A food effect trial involving administration of IMITREX Tablets 100 mg to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} and AUC were increased by 15% and 12%, respectively, when administered in the fed state.

Distribution: Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL is low, approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated. The apparent volume of distribution is 2.7 L/kg.

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

Elimination: The elimination half-life of sumatriptan is approximately 2.5 hours. Radiolabeled ^{14}C-sumatriptan administered orally is largely renally excreted (about 60%) with about 40% found in the feces. Most of the radiolabeled compound excreted in the urine is the major metabolite, indole acetic acid (IAA), which is inactive, or the IAA glucuronide. Only 3% of the dose can be recovered as unchanged sumatriptan.

Special 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).

Renal Impairment: The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined.

Hepatic Impairment: The liver plays an important role in the presystemic clearance of orally administered sumatriptan. Accordingly, the bioavailability of sumatriptan following oral administration may be markedly increased in patients with liver disease. In one small trial of patients with moderate liver impairment (n = 8) matched for sex, age, and weight with healthy subjects (n = 8), the hepatically-impaired patients had an approximately 70% increase in AUC and C_{max} and a T_{max} 40 minutes earlier compared to the healthy subjects.

The pharmacokinetics of sumatriptan in patients with severe hepatic impairment has not been studied. The use of IMITREX Tablets in this population is contraindicated *[see Contraindications (4) and Use in Specific Populations (8.6)]*.

Gender: In a trial comparing females to males, no pharmacokinetic differences were observed between genders for AUC, C_{max}, T_{max}, and half-life.

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

Drug Interaction Studies: *Monoamine Oxidase-A Inhibitors:* Treatment with MAO-A inhibitors generally leads to an increase of sumatriptan plasma levels *[see Contraindications (4) and Drug Interactions (7.2)]*.

Due to gut and hepatic metabolic first-pass effects, the increase of systemic exposure after co-administration of an MAO-A inhibitor with oral sumatriptan is greater than after co-administration of the MAO inhibitors with subcutaneous sumatriptan.

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

A small trial evaluating the effect of pretreatment with an MAO-A inhibitor on the bioavailability from a 25-mg oral sumatriptan tablet resulted in an approximately 7-fold increase in systemic exposure.

Alcohol: Alcohol consumed 30 minutes prior to sumatriptan ingestion had no effect on the pharmacokinetics of sumatriptan.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In carcinogenicity studies in mouse and rat, sumatriptan was administered orally for 78 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). There was no evidence in either species of an increase in tumors related to sumatriptan administration. Plasma exposures (AUC) at the highest doses tested were 20 and 8 times that in humans at the maximum recommended human dose (MRHD) of 200 mg/day.

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 (5, 50, 500 mg/kg/day) was administered orally to male and female rats prior to and throughout the mating period, there was a treatment-related decrease in fertility secondary to a decrease in mating in animals treated with doses greater than 5 mg/kg/day (less than the MRHD on a mg/m^2 basis). It is not clear whether this finding was due to an effect on males or females or both.

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. Plasma exposure at the lowest dose tested was approximately 2 times that in humans at the MRHD.

14 CLINICAL STUDIES

The efficacy of IMITREX Tablets in the acute treatment of migraine headaches was demonstrated in 3, randomized, double-blind, placebo-controlled trials. Patients enrolled in these 3 trials were predominately female (87%) and Caucasian (97%), with a mean age of 40 years (range of 18 to 65 years). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed up to 4 hours after dosing. Associated symptoms such as nausea, photophobia, and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours postdose. A second dose of IMITREX Tablets or other medication was allowed 4 to 24 hours after the initial treatment for recurrent headache. Acetaminophen was offered to patients in Trials 2 and 3 beginning at 2 hours after initial treatment if the migraine pain had not improved or worsened. Additional medications were allowed 4 to 24 hours after the initial treatment for recurrent headache or as rescue in all 3 trials. The frequency and time to use of these additional treatments were also determined. In all trials, doses of 25, 50, and 100 mg were compared with placebo in the treatment of migraine attacks. In 1 trial, doses of 25, 50, and 100 mg were also compared with each other.

In all 3 trials, the percentage of patients achieving headache response 2 and 4 hours after treatment was significantly greater among patients receiving IMITREX Tablets at all doses compared with those who received placebo. In 1 of the 3 trials, there was a statistically significant greater percentage of patients with headache response at 2 and 4 hours in the 50-mg or 100-mg group when compared with the 25-mg dose groups. There were no statistically significant differences between the 50-mg and 100-mg dose groups in any trial. The results from the 3 controlled clinical trials are summarized in Table 2.

Table 2. Percentage of Patients With Headache Response (Mild or No Headache) 2 and 4 Hours Following Treatment

	IMITREX Tablets 25 mg		IMITREX Tablets 50 mg		IMITREX Tablets 100 mg		Placebo	
	2 hr	4 hr	2 hr	4 hr	2 hr	4 hr	2 hr	4 hr
Trial 1	52%[a] (n = 298)	67%[a]	61%[a,b] (n = 296)	78%[a,b]	62%[a,b] (n = 296)	79%[a,b]	27% (n = 94)	38%
Trial 2	52%[a] (n = 66)	70%[a]	50%[a] (n = 62)	68%[a]	56%[a] (n = 66)	71%[a]	26% (n = 65)	38%
Trial 3	52%[a]	65%[a]	54%[a]	72%[a]	57%[a]	78%[a]	17%	19%

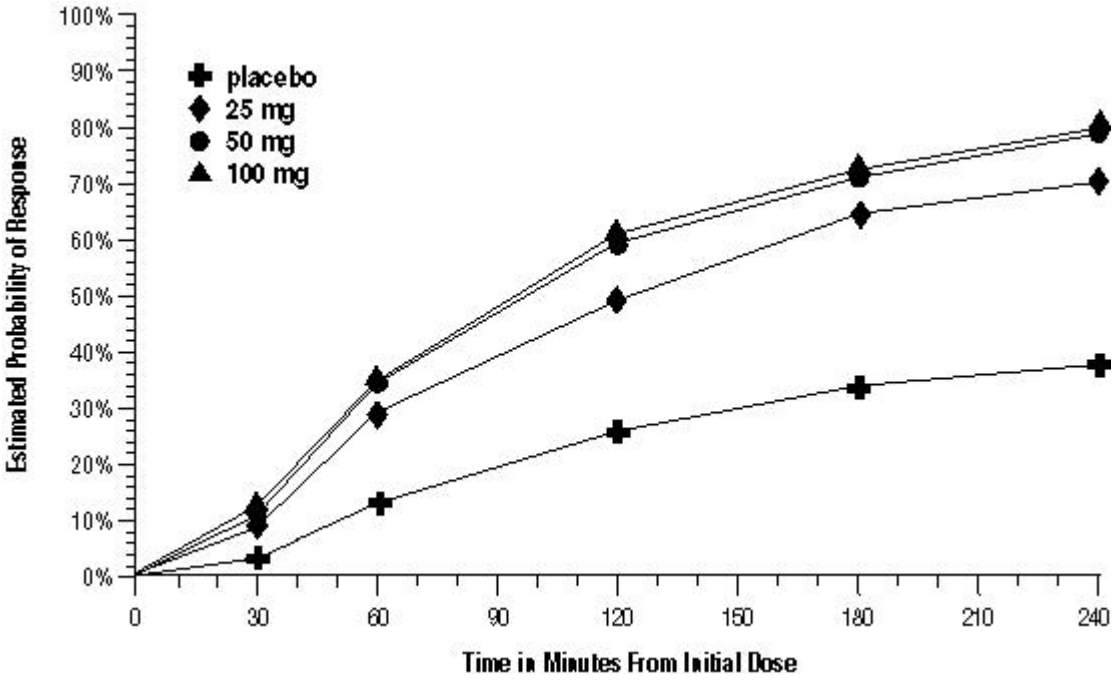
	(n = 48)	(n = 46)	(n = 46)	(n = 47)

[a] *P*<0.05 in comparison with placebo.

[b] *P*<0.05 in comparison with 25 mg.

The estimated probability of achieving an initial headache response over the 4 hours following treatment in pooled Trials 1, 2, and 3 is depicted in Figure 1.

Figure 1. Estimated Probability of Achieving Initial Headache Response Within 4 Hours of Treatment in Pooled Trials 1, 2, and 3[a]



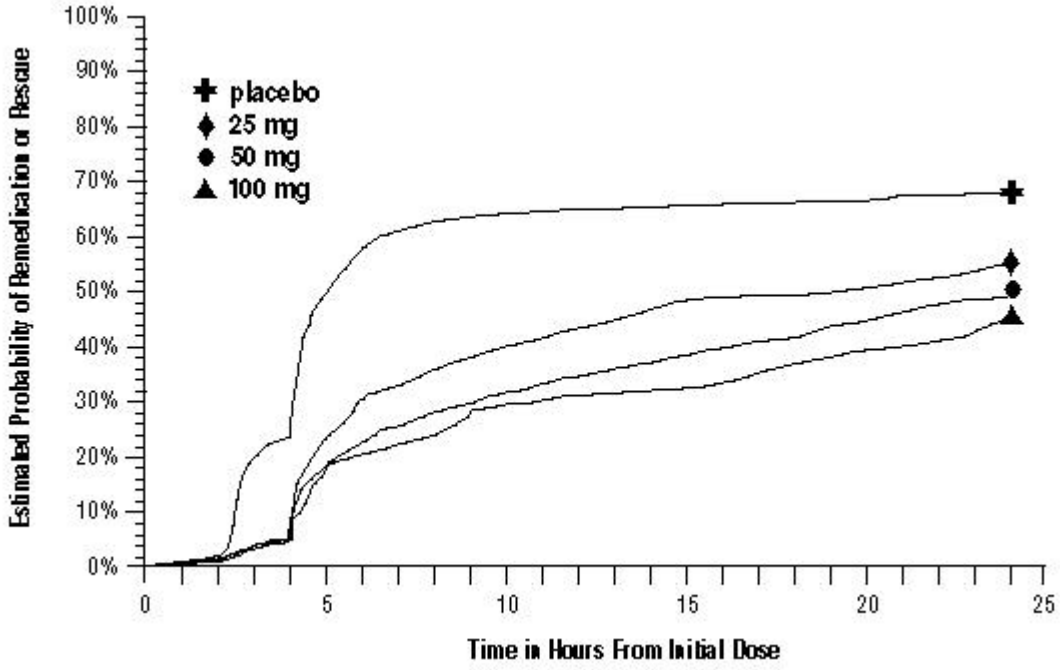
[a] The figure shows the probability over time of obtaining headache response (no or mild pain) following treatment with oral sumatriptan. The averages displayed are based on pooled data from the 3 clinical controlled trials providing evidence of efficacy. Kaplan-Meier plot with patients not achieving response and/or taking rescue within 240 minutes censored to 240 minutes.

For patients with migraine-associated nausea, photophobia, and/or phonophobia at baseline, there was a lower incidence of these symptoms at 2 hours (Trial 1) and at 4 hours (Trials 1, 2, and 3) following administration of IMITREX Tablets compared with placebo.

As early as 2 hours in Trials 2 and 3, or as early as 4 hours in Trial 1, through 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment

for pain relief in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2. The Estimated Probability of Patients Taking a Second Dose of IMITREX Tablets or Other Medication to Treat Migraine Over the 24 Hours Following the Initial Dose of Study Treatment in Pooled Trials 1, 2, and 3[a]



[a] Kaplan-Meier plot based on data obtained in the 3 clinical controlled trials providing evidence of efficacy with patients not using additional treatments censored to 24 hours. Plot also includes patients who had no response to the initial dose. No remedication was allowed within 2 hours postdose.

There is evidence that doses above 50 mg do not provide a greater effect than 50 mg. There was no evidence to suggest that treatment with IMITREX Tablets was associated with an increase in the severity of recurrent headaches. The efficacy of IMITREX Tablets was unaffected by presence of aura; duration of headache prior to treatment; gender, age, or weight of the subject; relationship to menses; or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants). There were insufficient data to assess the impact of race on efficacy.

16 HOW SUPPLIED/STORAGE AND HANDLING

IMITREX Tablets, 25 mg, 50 mg, and 100 mg of sumatriptan (base) as the succinate.

IMITREX Tablets, 25 mg, are white, triangular-shaped, film-coated tablets debossed with "I" on one side and "25" on the other in blister packs of 9 tablets (NDC 0173-0735-00).

IMITREX Tablets, 50 mg, are white, triangular-shaped, film-coated tablets debossed with "IMITREX 50" on one side and a chevron shape (^) on the other in blister packs of 9 tablets (NDC 0173-0736-01).

IMITREX Tablets, 100 mg, are pink, triangular-shaped, film-coated tablets debossed with "IMITREX 100" on one side and a chevron shape (^) on the other in blister packs of 9 tablets (NDC 0173-0737-01).

Store between 2°C and 30°C (36°F and 86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Risk of Myocardial Ischemia and/or Infarction, Prinzmetal's Angina, Other Vasospasm-Related Events, Arrhythmias, and Cerebrovascular Events: Inform patients that IMITREX Tablets 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 if 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)]*.

Anaphylactic/Anaphylactoid Reactions: Inform patients that anaphylactic/anaphylactoid reactions have occurred in patients receiving IMITREX Tablets. 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 IMITREX Tablets 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 IMITREX Tablets 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: Inform patients that IMITREX Tablets should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus *[see Use in Specific Populations (8.1)]*.

Nursing Mothers: Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed *[see Use in Specific Populations (8.3)]*.

Ability to Perform Complex Tasks: Treatment with IMITREX Tablets may cause somnolence and dizziness; instruct patients to evaluate their ability to perform complex tasks after administration of IMITREX Tablets.

IMITREX is a registered trademark of the GlaxoSmithKline group of companies.

GlaxoSmithKline
Research Triangle Park, NC 27709

IMT:XPI

Patient Information
IMITREX® (IM-i-trex)
(sumatriptan succinate)
Tablets

Read this Patient Information before you start taking IMITREX and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about IMITREX?

IMITREX can cause serious side effects, including:

Heart attack and other heart problems. Heart problems may lead to death.

Stop taking IMITREX and get emergency medical help right away if you have any of the following symptoms of a heart attack:

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

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

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

What is IMITREX?

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

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

IMITREX is not used to prevent or decrease the number of migraine headaches you have.

It is not known if IMITREX is safe and effective to treat cluster headaches.

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

Who should not take IMITREX?

Do not take IMITREX if you have:

- heart problems or a history of heart problems
- narrowing of blood vessels to your legs, arms, stomach, or kidneys (peripheral vascular disease)

- uncontrolled high blood pressure
- severe liver problems
- hemiplegic migraines or basilar migraines. If you are not sure if you have these types of migraines, ask your healthcare provider.
- had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation
- taken any of the following medicines in the last 24 hours:
  - almotriptan (AXERT®)
  - eletriptan (RELPAX®)
  - frovatriptan (FROVA®)
  - naratriptan (AMERGE®)
  - rizatriptan (MAXALT®, MAXALT-MLT®)
  - sumatriptan and naproxen (TREXIMET®)
  - ergotamines (CAFERGOT®, ERGOMAR®, MIGERGOT®)
  - dihydroergotamine (D.H.E. 45®, MIGRANAL®)

  Ask your healthcare provider if you are not sure if your medicine is listed above.
- an allergy to sumatriptan or any of the ingredients in IMITREX. See the end of this leaflet for a complete list of ingredients in IMITREX.

What should I tell my healthcare provider before taking IMITREX?

Before you take IMITREX, tell your healthcare provider about all of your medical conditions, including if you:

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

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

IMITREX and certain other medicines can affect each other, causing serious side effects.

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

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

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

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

How should I take IMITREX?

- Certain people should take their first dose of IMITREX in their healthcare provider's office or in another medical setting. Ask your healthcare provider if you should take your first dose in a medical setting.
- Take IMITREX exactly as your healthcare provider tells you to take it.
- Your healthcare provider may change your dose. Do not change your dose without first talking to your healthcare provider.
- Take IMITREX Tablets whole with water or other liquids.
- If you do not get any relief after your first tablet, do not take a second tablet without first talking with your healthcare provider.
- If your headache comes back or you only get some relief from your headache, you can take a second tablet 2 hours after the first tablet.
- Do not take more than 200 mg of IMITREX Tablets in a 24-hour period.
- If you take too much IMITREX, call your healthcare provider or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you take IMITREX so you can talk with your healthcare provider about how IMITREX is working for you.

What should I avoid while taking IMITREX?

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

What are the possible side effects of IMITREX?

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

These serious side effects include:

- changes in color or sensation in your fingers and toes (Raynaud's syndrome)
- stomach and intestinal problems (gastrointestinal and colonic ischemic events). Symptoms of gastrointestinal and colonic ischemic events include:
  - sudden or severe stomach pain
  - stomach pain after meals
  - weight loss
  - nausea or vomiting
  - constipation or diarrhea
  - bloody diarrhea
  - fever
- problems with blood circulation to your legs and feet (peripheral vascular ischemia). Symptoms of peripheral vascular ischemia include:
  - cramping and pain in your legs or hips
  - feeling of heaviness or tightness in your leg muscles
  - burning or aching pain in your feet or toes while resting
  - numbness, tingling, or weakness in your legs
  - cold feeling or color changes in 1 or both legs or feet
- hives (itchy bumps); swelling of your tongue, mouth, or throat
- medication overuse headaches. Some people who use too many IMITREX tablets may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with IMITREX.
- serotonin syndrome. Serotonin syndrome is a rare but serious problem that can happen in people using IMITREX, especially if IMITREX 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 IMITREX who have never had seizures before. Talk with your healthcare provider about your chance of having seizures while you take IMITREX.

The most common side effects of IMITREX Tablets include:

- tingling or numbness in your fingers or toes
- warm or cold feeling
- feeling weak, drowsy, or tired
- pain, discomfort, or stiffness in your neck, throat, jaw, or chest
- dizziness

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 IMITREX. For more information, ask your healthcare provider or pharmacist.

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

How should I store IMITREX Tablets?

Store IMITREX between 36°F to 86°F (2°C to 30°C).

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

General information about the safe and effective use of IMITREX.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use IMITREX for a condition for which it was not prescribed. Do not give IMITREX 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 IMITREX. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about IMITREX that is written for healthcare professionals.

For more information, go to www.gsk.com or call 1-888-825-5249.

What are the ingredients in IMITREX Tablets?

Active ingredient: sumatriptan succinate

Inactive ingredients: croscarmellose sodium, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, and sodium bicarbonate

100-mg tablets also contain hypromellose, iron oxide, titanium dioxide, and triacetin.

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

GlaxoSmithKline
Research Triangle Park, NC 27709

Month Year
IMT:xPIL

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IMITREX safely and effectively. See full prescribing information for IMITREX.

IMITREX (sumatriptan) Nasal Spray
Initial U.S. Approval: 1992

----------INDICATIONS AND USAGE----------

IMITREX 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 headache has been established. (1)
- Not indicated for the prophylactic therapy of migraine attacks. (1)
- Not indicated for the treatment of cluster headache. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Single dose of 5 mg, 10 mg, or 20 mg of nasal spray. (2)
- A second dose should only be considered if some response to the first dose was observed. Separate doses by at least 2 hours. (2)
- Maximum dose in a 24-hour period: 40 mg. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------

Nasal spray: 5 mg and 20 mg (3, 16)

----------CONTRAINDICATIONS----------

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

---------- WARNINGS AND PRECAUTIONS ----------

- Myocardial ischemia/infarction and Prinzmetal's angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors. (5.1)
- Arrhythmias: Discontinue IMITREX 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 IMITREX if occurs. (5.4)
- Gastrointestinal ischemic reactions and peripheral vasospastic reactions: Discontinue IMITREX if occurs. (5.5)
- Medication overuse headache: Detoxification may be necessary. (5.6)
- Serotonin syndrome: Discontinue IMITREX if occurs. (5.7)
- Seizures: Use with caution in patients with epilepsy or a lowered seizure threshold. (5.11)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (≥1% and >placebo) were burning sensation, disorder/discomfort of nasal cavity/sinuses, throat discomfort, nausea and/or vomiting, bad/unusual taste, and dizziness/vertigo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

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

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

Revised: XX/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IMITREX® Nasal Spray 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 headache has been established. If a patient has no response to the first migraine attack treated with IMITREX, reconsider the diagnosis of migraine before IMITREX is administered to treat any subsequent attacks.
- IMITREX is not indicated for the prevention of migraine attacks.
- Safety and effectiveness of IMITREX Nasal Spray have not been established for cluster headache.

2 DOSAGE AND ADMINISTRATION

The recommended adult dose of IMITREX Nasal Spray for the acute treatment of migraine is 5 mg, 10 mg, or 20 mg. The 20-mg dose may provide a greater effect than the 5-mg and 10-mg doses, but may have a greater risk of adverse reactions *[see Clinical Studies (14)]*.

The 5-mg and 20-mg doses are given as a single spray in 1 nostril. The 10-mg dose may be achieved by the administration of a single 5-mg dose in each nostril.

If the migraine has not resolved by 2 hours after taking IMITREX Nasal Spray, or returns after a transient improvement, 1 additional dose may be administered at least 2 hours after the first dose. The maximum daily dose is 40 mg in a 24-hour period.

The safety of treating an average of more than 4 headaches in a 30-day period has not been established.

3 DOSAGE FORMS AND STRENGTHS

Unit dose nasal spray devices containing 5 mg or 20 mg sumatriptan.

4 CONTRAINDICATIONS

IMITREX Nasal Spray 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, transient ischemic attack (TIA), or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke *[see Warnings and Precautions (5.4)]*
- Peripheral vascular disease *[see Warnings and Precautions (5.5)]*
- Ischemic bowel disease *[see Warnings and Precautions (5.5)]*
- Uncontrolled hypertension *[see Warnings and Precautions (5.8)]*
- Recent use (i.e., within 24 hours) of ergotamine-containing medication, ergot-type medication (such as dihydroergotamine or methysergide), or another 5-hydroxytryptamine$_1$ (5-HT$_1$) agonist *[see Drug Interactions (7.1, 7.3)]*
- Concurrent administration of a monoamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*
- Hypersensitivity to IMITREX (angioedema and anaphylaxis seen) *[see Warnings and Precautions (5.10)]*
- 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 IMITREX Nasal Spray 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 IMITREX Nasal Spray. Some of these reactions occurred in patients without known CAD. IMITREX Nasal Spray 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 IMITREX Nasal Spray. If there is evidence of CAD or coronary artery vasospasm, IMITREX Nasal Spray is contraindicated. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first dose of IMITREX Nasal Spray in a medically supervised setting and performing an electrocardiogram (ECG) immediately following administration of IMITREX Nasal Spray. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of IMITREX Nasal Spray.

5.2 Arrhythmias

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

occur. IMITREX Nasal Spray 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 may occur after treatment with IMITREX Nasal Spray and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. The use of IMITREX Nasal Spray is contraindicated in patients with CAD and those with Prinzmetal's variant angina.

5.4 Cerebrovascular Events

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

Before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, exclude other potentially serious neurological conditions. IMITREX Nasal Spray is contraindicated in patients with a history of stroke or TIA.

5.5 Other Vasospasm Reactions

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

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

5.6 Medication Overuse Headache

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

5.7 Serotonin Syndrome

Serotonin syndrome may occur with IMITREX Nasal Spray, 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 IMITREX Nasal Spray if serotonin syndrome is suspected.

5.8 Increase in Blood Pressure

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

5.9 Local Irritation

Local irritative symptoms such as burning, numbness, paresthesia, discharge, and pain or soreness were reported in approximately 5% of patients in controlled clinical trials and were noted to be severe in about 1%. The symptoms were transient and generally resolved in less than 2 hours. Limited examinations of the nose and throat did not reveal any clinically noticeable injury in these patients. The consequences of extended and repeated use of IMITREX Nasal Spray on the nasal and/or respiratory mucosa have not been systematically evaluated in patients.

5.10 Anaphylactic/Anaphylactoid Reactions

Anaphylactic/anaphylactoid reactions have occurred in patients receiving IMITREX. 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. IMITREX Nasal Spray is contraindicated in patients with a history of hypersensitivity reaction to IMITREX.

5.11 Seizures

Seizures have been reported following administration of IMITREX. 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. IMITREX Nasal Spray 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 adverse reactions are discussed in more detail in other sections of the

prescribing information:

- 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)]*
- Local irritation *[see Warnings and Precautions (5.9)]*
- Hypersensitivity reactions *[see Contraindications (4) and Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

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

Table 1 lists adverse reactions that occurred in worldwide placebo-controlled clinical trials in 3,419 patients with migraine. Only treatment-emergent adverse reactions that occurred at a frequency of 1% or more in the group treated with IMITREX Nasal Spray 20 mg and that occurred at a frequency greater than the placebo group are included in Table 1.

Table 1. Adverse Reactions Reported by at Least 1% of Patients and at a Greater Frequency Than Placebo in Controlled Migraine Clinical Trials

	Percent of Patients Reporting			
Adverse Reaction	**IMITREX Nasal Spray 5 mg (n = 496)**	**IMITREX Nasal Spray 10 mg (n = 1,007)**	**IMITREX Nasal Spray 20 mg (n = 1,212)**	**Placebo (n = 704)**
Atypical sensations				
Burning sensation	0.4	0.6	1.4	0.1
Ear, nose, and throat				
Disorder/discomfort of nasal cavity/sinuses	2.8	2.5	3.8	2.4
Throat discomfort	0.8	1.8	2.4	0.9
Gastrointestinal				
Nausea and/or vomiting	12.2	11.0	13.5	11.3
Neurological				
Bad/unusual taste	13.5	19.3	24.5	1.7
Dizziness/vertigo	1.0	1.7	1.4	0.9

The incidence of adverse reactions in controlled clinical trials was not affected by gender, weight, or age of the patients; use of prophylactic medications; or presence of aura. There were insufficient data to assess the impact of race on the incidence of adverse reactions.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of IMITREX Tablets, IMITREX Nasal Spray, and IMITREX 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. These reactions have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to IMITREX or a combination of these factors.

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 IMITREX Nasal Spray within 24 hours of each other is contraindicated.

7.2 Monoamine Oxidase-A Inhibitors

MAO-A inhibitors increase systemic exposure by up to 7-fold. Therefore, the use of IMITREX Nasal Spray in patients receiving MAO-A inhibitors is contraindicated *[see Clinical Pharmacology (12.3)]*.

7.3 Other 5-HT_1 Agonists

Because their vasospastic effects may be additive, co-administration of IMITREX Nasal Spray and other 5-HT_1 agonists (e.g., triptans) within 24 hours of each other is contraindicated.

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled trials in pregnant women. In developmental toxicity studies in rats and rabbits, oral administration of sumatriptan to pregnant animals was associated with embryolethality, fetal abnormalities, and pup mortality. When administered by the intravenous route to pregnant rabbits, sumatriptan was embryolethal. Developmental toxicity studies of sumatriptan by the intranasal route have not been conducted. IMITREX Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 embryolethality and fetal cervicothoracic vascular and skeletal abnormalities. Intravenous administration of sumatriptan to pregnant rabbits during the period of organogenesis resulted in an increased incidence of embryolethality. 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.

8.3 Nursing Mothers

Sumatriptan is excreted in human milk following subcutaneous administration. Infant exposure to sumatriptan can be minimized by avoiding breastfeeding for 12 hours after treatment with IMITREX Nasal Spray.

8.4 Pediatric Use

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

Two controlled clinical trials evaluated IMITREX Nasal Spray (5 to 20 mg) in 1,248 adolescent migraineurs aged 12 to 17 years who treated a single attack. The trials did not establish the efficacy of IMITREX Nasal Spray compared with placebo in the treatment of migraine in adolescents. 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 IMITREX (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These trials did not establish the efficacy of oral IMITREX compared with placebo in the treatment of migraine in adolescents. 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 adolescents.

Postmarketing experience documents that serious adverse reactions have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal IMITREX. 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 IMITREX; 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 IMITREX are not presently available.

8.5 Geriatric Use

Clinical trials of IMITREX Nasal Spray did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

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

10 OVERDOSAGE

In clinical trials, the highest single doses of IMITREX Nasal Spray administered without significant reactions were 40 mg to 12 volunteers and 40 mg to 85 subjects with migraine, which is twice the highest single recommended dose. In addition, 12 volunteers were administered a total daily dose of 60 mg (20 mg 3 times daily) for 3.5 days without significant adverse reactions.

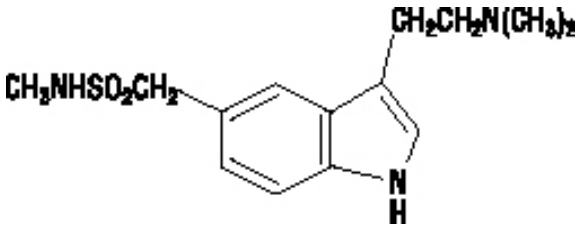
Overdose in animals has been fatal and has been heralded by convulsions, tremor, paralysis, inactivity, ptosis, erythema of the extremities, abnormal respiration, cyanosis, ataxia, mydriasis, salivation, and lacrimation.

The elimination half-life of sumatriptan is approximately 2 hours *[see Clinical Pharmacology (12.3)]*, and therefore monitoring of patients after overdose with IMITREX Nasal Spray 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

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



The empirical formula is $C_{14}H_{21}N_3O_2S$, representing a molecular weight of 295.4. Sumatriptan is a white to off-white powder that is readily soluble in water and in saline.

Each IMITREX Nasal Spray contains 5 or 20 mg of sumatriptan in a 100-µL unit dose aqueous buffered solution containing monobasic potassium phosphate NF, anhydrous dibasic sodium phosphate USP, sulfuric acid NF, sodium hydroxide NF, and purified water USP. The pH of the solution is approximately 5.5. The osmolality of the solution is 372 or 742 mOsmol for the 5- and 20-mg IMITREX Nasal Spray, respectively.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

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

Heart Rate: Transient increases in blood pressure observed in some patients 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

Absorption and Bioavailability: In a trial of 20 female volunteers, the mean maximum concentration following a 5- and 20-mg intranasal dose was 5 and 16 ng/mL, respectively. The mean C_{max} following a 6-mg subcutaneous injection is 71 ng/mL (range: 49 to 110 ng/mL). The mean C_{max} is 18 ng/mL (range: 7 to 47 ng/mL) following oral dosing with 25 mg and 51 ng/mL (range: 28 to 100 ng/mL) following oral dosing with 100 mg of sumatriptan. In a trial of 24 male volunteers, the bioavailability relative to subcutaneous injection was low, approximately 17%, primarily due to presystemic metabolism and partly due to incomplete absorption.

Clinical and pharmacokinetic data indicate that administration of two 5-mg doses, 1 dose in each nostril, is equivalent to administration of a single 10-mg dose in 1 nostril.

Distribution: Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL, is low, approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated. The apparent volume of distribution is 2.7 L/kg.

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

Elimination: The elimination half-life of sumatriptan administered as a nasal spray is approximately 2 hours, similar to the half-life seen after subcutaneous injection. Only 3% of the

dose is excreted in the urine as unchanged sumatriptan; 42% of the dose is excreted as the major metabolite, the indole acetic acid analogue of sumatriptan. The total plasma clearance is approximately 1,200 mL/min.

Special 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). Intranasal sumatriptan has not been evaluated for age differences.

Renal Impairment: The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined.

Hepatic Impairment: The effect of mild to moderate hepatic disease on the pharmacokinetics of the intranasal formulation of sumatriptan has not been evaluated. Sumatriptan bioavailability following intranasal administration is 17%, similar to that after oral administration (15%). Following oral administration, an approximately 70% increase in C_{max} and AUC was observed in one small trial of patients with moderate liver impairment (n = 8) matched for sex, age and weight with healthy subjects (n = 8). Similar changes can be expected following intranasal administration.

The pharmacokinetics of sumatriptan in patients with severe hepatic impairment has not been studied. The use of IMITREX Nasal Spray in patients with severe hepatic impairment is contraindicated *[see Contraindications (4)]*.

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

Drug Interaction Studies: *Monoamine Oxidase-A Inhibitors:* Treatment with MAO-A inhibitors generally leads to an increase of sumatriptan plasma levels *[see Contraindications (4) and Drug Interactions (7.2)]*. MAO inhibitors interaction studies have not been performed with intranasal sumatriptan.

Due to gut and hepatic metabolic first-pass effects, the increase of systemic exposure after co-administration of an MAO-A inhibitor with oral sumatriptan is greater than after co-administration of the MAO inhibitors with subcutaneous sumatriptan. The effects of an MAO inhibitor on systemic exposure after intranasal sumatriptan would be expected to be greater than the effect after subcutaneous sumatriptan but smaller than the effect after oral sumatriptan because only swallowed drug would be subject to first-pass effects.

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

A small trial evaluating the effect of pretreatment with an MAO-A inhibitor on the bioavailability from a 25-mg oral sumatriptan tablet resulted in an approximately 7-fold increase in systemic exposure.

Xylometazoline: An in vivo drug interaction trial indicated that 3 drops of xylometazoline (0.1% w/v), a decongestant, administered 15 minutes prior to a 20-mg nasal dose of sumatriptan did not alter the pharmacokinetics of sumatriptan.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In carcinogenicity studies in mouse and rat in which sumatriptan was administered orally for 78 and 104 weeks, respectively, there was no evidence in either species of an increase in tumors related to sumatriptan administration.

Carcinogenicity studies of sumatriptan using the nasal route have not been conducted.

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 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. When sumatriptan (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.

Fertility studies of sumatriptan using the intranasal route have not been conducted.

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

The efficacy of IMITREX Nasal Spray in the acute treatment of migraine headaches was demonstrated in 8, randomized, double-blind, placebo-controlled trials, of which 5 used the recommended dosing regimen and used the marketed formulation. Patients enrolled in these 5 trials were predominately female (86%) and Caucasian (95%), with a mean age of 41 years (range of 18 to 65 years). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to

mild or no pain, was assessed up to 2 hours after dosing. Associated symptoms such as nausea, photophobia, and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours postdose. A second dose of IMITREX Nasal Spray or other medication was allowed 2 to 24 hours after the initial treatment for recurrent headache. The frequency and time to use of these additional treatments were also determined. In all trials, doses of 10 and 20 mg were compared with placebo in the treatment of 1 to 3 migraine attacks. Patients received doses as a single spray into 1 nostril. In 2 trials, a 5-mg dose was also evaluated.

In all 5 trials utilizing the market formulation and recommended dosage regimen, the percentage of patients achieving headache response 2 hours after treatment was significantly greater among patients receiving IMITREX Nasal Spray at all doses (with one exception) compared with those who received placebo. In 4 of the 5 trials, there was a statistically significant greater percentage of patients with headache response at 2 hours in the 20-mg group when compared with the lower dose groups (5 and 10 mg). There were no statistically significant differences between the 5- and 10-mg dose groups in any trial. The results from the 5 controlled clinical trials are summarized in Table 2. Note that, in general, comparisons of results obtained in trials conducted under different conditions by different investigators with different samples of patients are ordinarily unreliable for purposes of quantitative comparison.

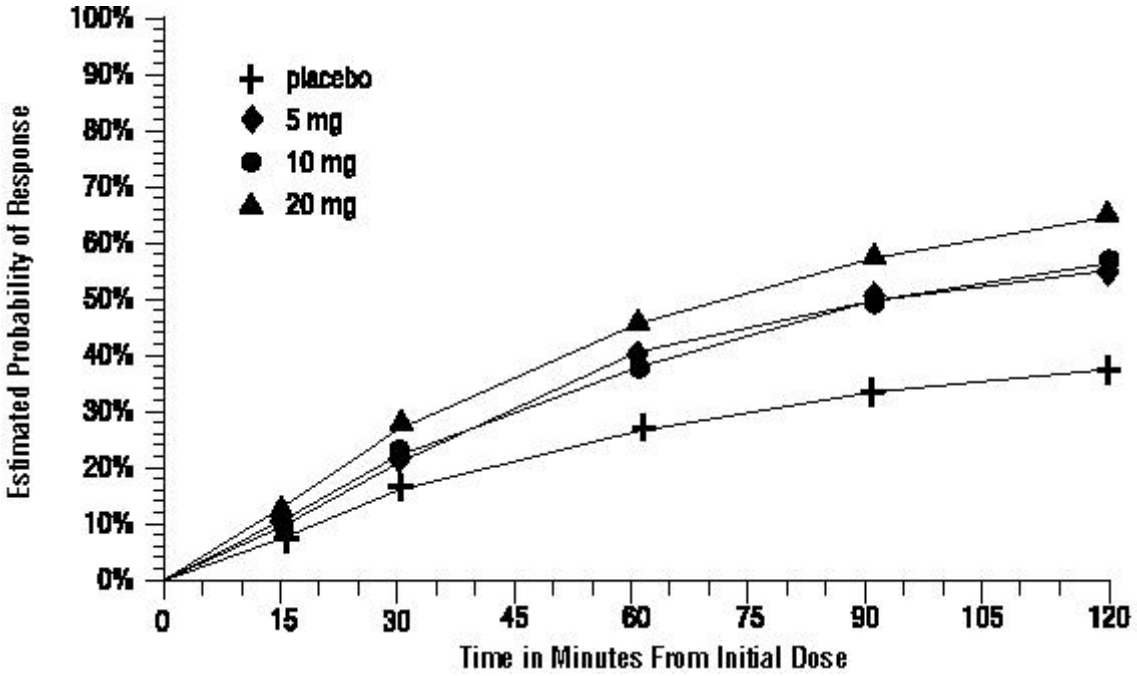
Table 2. Percentage of Patients With Headache Response (No or Mild Pain) 2 Hours Following Treatment

	IMITREX Nasal Spray 5 mg	**IMITREX Nasal Spray 10 mg**	**IMITREX Nasal Spray 20 mg**	**Placebo**
Trial 1	49%[a] (n = 121)	46%[a] (n = 112)	64%[a,b,c] (n = 118)	25% (n = 63)
Trial 2	Not applicable	44%[a] (n = 273)	55%[a,b] (n = 277)	25% (n = 138)
Trial 3	Not applicable	54%[a] (n = 106)	63%[a] (n = 202)	35% (n = 100)
Trial 4	Not applicable	43% (n = 106)	62%[a,b] (n = 215)	29% (n = 112)
Trial 5[d]	45%[a] (n = 296)	53%[a] (n = 291)	60%[a,c] (n = 286)	36% (n = 198)

[a] $P<0.05$ in comparison with placebo.
[b] $P<0.05$ in comparison with 10 mg.
[c] $P<0.05$ in comparison with 5 mg.
[d] Data are for attack 1 only of multi-attack trial for comparison.

The estimated probability of achieving an initial headache response over the 2 hours following treatment is depicted in Figure 1.

Figure 1. Estimated Probability of Achieving Initial Headache Response Within 120 Minutes[a]

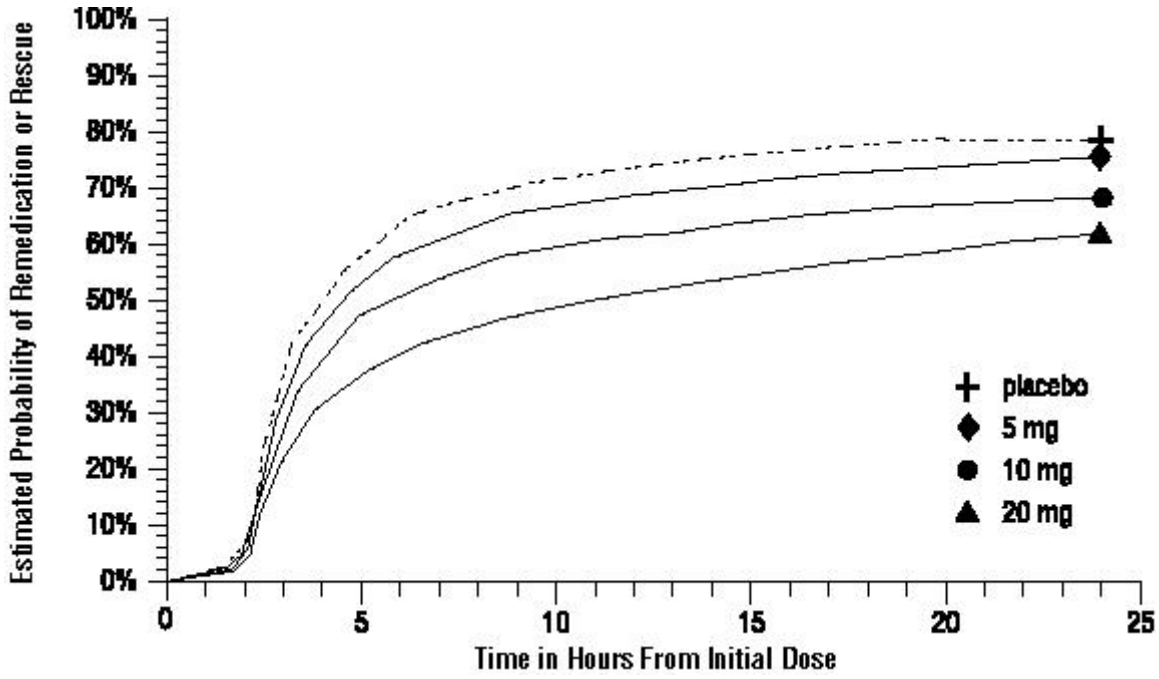


[a] The figure shows the probability over time of obtaining headache response (no or mild pain) following treatment with intranasal sumatriptan. The averages displayed are based on pooled data from the 5 clinical controlled trials providing evidence of efficacy. Kaplan-Meier plot with patients not achieving response within 120 minutes censored to 120 minutes.

For patients with migraine-associated nausea, photophobia, and phonophobia at baseline, there was a lower incidence of these symptoms at 2 hours following administration of IMITREX Nasal Spray compared with placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain relief in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2. The Estimated Probability of Patients Taking a Second Dose or Other Medication for Migraine Over the 24 Hours Following the Initial Dose of Study Treatment[a]



[a] Kaplan-Meier plot based on data obtained in the 3 clinical controlled trials providing evidence of efficacy with patients not using additional treatments censored to 24 hours. Plot also includes patients who had no response to the initial dose. No remedication was allowed within 2 hours postdose.

There is evidence that doses above 20 mg do not provide a greater effect than 20 mg. There was no evidence to suggest that treatment with sumatriptan was associated with an increase in the severity of recurrent headaches. The efficacy of IMITREX Nasal Spray was unaffected by presence of aura; duration of headache prior to treatment; gender, age, or weight of the subject; or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants). There were insufficient data to assess the impact of race on efficacy.

16 HOW SUPPLIED/STORAGE AND HANDLING

IMITREX Nasal Spray 5 mg (NDC 0173-0524-00) and 20 mg (NDC 0173-0523-00) are each supplied in boxes of 6 nasal spray devices. Each unit dose spray supplies 5 mg and 20 mg, respectively, of sumatriptan.

Store between 2°C and 30°C (36°F and 86°F). Protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Risk of Myocardial Ischemia and/or Infarction, Prinzmetal's Angina, Other Vasospasm-Related Events, Arrhythmias, and Cerebrovascular Events: Inform patients that IMITREX Nasal Spray 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 if 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)]*.

Anaphylactic/Anaphylactoid Reactions: Inform patients that anaphylactic/anaphylactoid reactions have occurred in patients receiving IMITREX Nasal Spray. 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 (5.10)]*.

Concomitant Use With Other Triptans or Ergot Medications: Inform patients that use of IMITREX Nasal Spray within 24 hours of another triptan or an ergot-type medication (including dihydroergotamine or methysergide) is contraindicated *[see Contraindications (4) and Drug Interactions (7.1, 7.3)]*.

Serotonin Syndrome: Caution patients about the risk of serotonin syndrome with the use of IMITREX Nasal Spray or other triptans, particularly during combined use with SSRIs, SNRIs, TCAs, and MAO inhibitors *[see Warnings and Precautions (5.7) and 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: Inform patients that IMITREX Nasal Spray should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus *[see Use in Specific Populations (8.1)]*.

Nursing Mothers: Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed *[see Use in Specific Populations (8.3)]*.

Ability to Perform Complex Tasks: Treatment with IMITREX Nasal Spray may cause somnolence and dizziness; instruct patients to evaluate their ability to perform complex tasks after administration of IMITREX Nasal Spray.

Local Irritation: Inform patents that they may experience local irritation of their nose and throat. The symptoms will generally resolve in less than 2 hours.

How to Use IMITREX Nasal Spray: Provide patients instruction on the proper use of IMITREX Nasal Spray. Caution patients to avoid spraying the contents of the device in their eyes.

IMITREX is a registered trademark of the GlaxoSmithKline group of companies.

GlaxoSmithKline
Research Triangle Park, NC 27709

IMN:xPI

Patient Information
IMITREX® (IM-i-trex)
(sumatriptan)
Nasal Spray

Read this Patient Information before you start using IMITREX and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about IMITREX?

IMITREX can cause serious side effects, including:

Heart attack and other heart problems. Heart problems may lead to death.

Stop taking IMITREX and get emergency medical help right away if you have any of the following symptoms of a heart attack:

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

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

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

What is IMITREX?

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

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

IMITREX is not used to prevent or decrease the number of migraine headaches you have.

It is not known if IMITREX is safe and effective to treat cluster headaches.

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

Who should not use IMITREX?

Do not use IMITREX if you have:

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

- naratriptan (AMERGE®)
- rizatriptan (MAXALT®, MAXALT-MLT®)
- sumatriptan and naproxen (TREXIMET®)
- ergotamines (CAFERGOT®, ERGOMAR®, MIGERGOT®)
- dihydroergotamine (D.H.E. 45®, MIGRANAL®)

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

- an allergy to sumatriptan or any of the ingredients in IMITREX. See below for a complete list of ingredients in IMITREX.

What should I tell my healthcare provider before using IMITREX?

Before you use IMITREX, tell your healthcare provider about all of your medical conditions, including if you:

- have high blood pressure
- have high cholesterol
- have diabetes
- smoke
- are overweight
- have heart problems or family history of heart problems or stroke
- have kidney problems
- have liver problems
- have had epilepsy or seizures
- are not using effective birth control
- become pregnant while taking IMITREX
- are breastfeeding or plan to breastfeed. IMITREX passes into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you use IMITREX.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

IMITREX and certain other medicines can affect each other, causing serious side effects.

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

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

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

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

How should I use IMITREX?

- Certain people should use their first dose of IMITREX in their healthcare provider's office or in another medical setting. Ask your healthcare provider if you should use your first dose in a medical setting.
- Use IMITREX exactly as your healthcare provider tells you to use it.
- Your healthcare provider may change your dose. Do not change your dose without first talking with your healthcare provider.
- If you do not get any relief after your first nasal spray, do not use a second nasal spray without first talking with your healthcare provider.
- If your headache comes back after the first nasal spray or you only get some relief from your headache, you can use a second nasal spray 2 hours after the first nasal spray.
- Do not use more than 40 mg of IMITREX Nasal Spray in a 24-hour period.
- It is not known how using IMITREX Nasal Spray for a long time affects the nose and throat.
- If you use too much IMITREX, call your healthcare provider or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you use IMITREX so you can talk with your healthcare provider about how IMITREX is working for you.

What should I avoid while using IMITREX?

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

What are the possible side effects of IMITREX?

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

These serious side effects include:

- changes in color or sensation in your fingers and toes (Raynaud's syndrome)
- stomach and intestinal problems (gastrointestinal and colonic ischemic events). Symptoms of gastrointestinal and colonic ischemic events include:
  - sudden or severe stomach pain
  - stomach pain after meals
  - weight loss
  - nausea or vomiting
  - constipation or diarrhea
  - bloody diarrhea
  - fever
- problems with blood circulation to your legs and feet (peripheral vascular ischemia). Symptoms of peripheral vascular ischemia include:
  - cramping and pain in your legs or hips
  - feeling of heaviness or tightness in your leg muscles
  - burning or aching pain in your feet or toes while resting
  - numbness, tingling, or weakness in your legs
  - cold feeling or color changes in 1 or both legs or feet
- hives (itchy bumps); swelling of your tongue, mouth, or throat
- medication overuse headaches. Some people who use too many IMITREX nasal sprays may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with IMITREX.
- serotonin syndrome. Serotonin syndrome is a rare but serious problem that can happen in people using IMITREX, especially if IMITREX 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 IMITREX who have never had seizures before. Talk with your healthcare provider about your chance of having seizures while you take IMITREX.

The most common side effects of IMITREX Nasal Spray include:

- unusual or bad taste in your mouth
- nausea and/or vomiting
- discomfort of your throat or nose
- dizziness
- warm, hot, burning feeling

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 IMITREX. For more information, ask your healthcare provider or pharmacist.

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

How should I store IMITREX Nasal Spray?

- Store IMITREX between 36°F to 86°F (2°C to 30°C).
- Store your medicine away from light.

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

General information about the safe and effective use of IMITREX.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use IMITREX for a condition for which it was not prescribed. Do not give IMITREX 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 IMITREX. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about IMITREX that is written for healthcare professionals.

For more information, go to www.gsk.com or call 1-888-825-5249.

What are the ingredients in IMITREX Nasal Spray?

Active ingredient: sumatriptan

Inactive ingredients: monobasic potassium phosphate NF, anhydrous dibasic sodium phosphate USP, sulfuric acid NF, sodium hydroxide NF, and purified water USP.

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

GlaxoSmithKline
Research Triangle Park, NC 27709

Month Year
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