CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-132/S-015

APPROVED LABELING

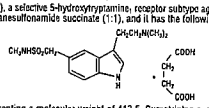
PRESCRIBING INFORMATION
4153251

IMITREX®
(sumatriptan succinate)
Tablets

IMITREX® (sumatriptan succinate) Tablets

DESCRIPTION

IMITREX Tablets contain sumatriptan (as the succinate), a selective 5-hydroxytryptamine$_1$ receptor subtype 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 $C_{14}H_{21}N_3O_2S \cdot C_4H_4O_4$, 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.

CLINICAL PHARMACOLOGY

Mechanism of Action: Sumatriptan is an agonist for a vascular 5-hydroxytryptamine$_1$ receptor subtype (probably a member of the 5-HT_{1D} family) having only a weak affinity for 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 receptors and no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT_3, 5-HT_4, or 5-HT_1 receptor subtypes or at alpha$_1$-, alpha$_2$-, or beta-adrenergic; dopamine$_1$; dopamine$_2$; muscarinic; or benzodiazepine receptors.

The vascular 5-HT_1 receptor subtype that sumatriptan activates is present on cranial arteries in both dog and primate, on the human basilar artery, and in the vasculature of human dura mater and mediates vasoconstriction. This action in humans correlates with the relief of migraine headache. In addition to causing vasoconstriction, experimental data from animal studies show that sumatriptan also activates 5-HT_1 receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels. Such an action may also contribute to the antimigrainous effect of sumatriptan in humans.

In the anesthetized dog, sumatriptan selectively reduces the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. In the cat, sumatriptan selectively constricts the carotid arteriovenous anastomoses while having little effect on blood flow or resistance in cerebral or extracerebral tissues.

Pharmacokinetics: 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 to 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 study 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.

Plasma protein binding is low (14% to 21%). The effect of sumatriptan on the protein binding of other drugs has not been evaluated, but would be expected to be minor, given the low rate of protein binding. The apparent volume of distribution is 2.4 L/kg.

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.

In vitro studies with human microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme, and inhibitors of that enzyme may alter sumatriptan pharmacokinetics to increase systemic exposure. No significant effect was seen with an MAO-B inhibitor (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions).

Special Populations: ***Renal Impairment:*** The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined, but little clinical effect would be expected as sumatriptan is largely metabolized to an inactive substance.

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 1 small study of hepatically impaired patients ($N = 8$) matched for sex, age, and weight with healthy subjects, 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 (see DOSAGE AND ADMINISTRATION).

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

Gender: In a study 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 sumatriptan were similar in black ($N = 34$) and Caucasian ($N = 38$) healthy male subjects.

Drug Interactions: ***Monoamine Oxidase Inhibitors:*** Treatment with MAO-A inhibitors generally leads to an increase of sumatriptan plasma levels (see CONTRAINDICATIONS and PRECAUTIONS).

Due to gut and hepatic metabolic first-pass effects, the increase of systemic exposure after coadministration of an MAO-A inhibitor with oral sumatriptan is greater than after coadministration of the monoamine oxidase inhibitors (MAOI) with subcutaneous sumatriptan. In a study of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of subcutaneous sumatriptan. Under the conditions of this experiment, the result was a 2-fold increase in the area under the sumatriptan plasma concentration x time curve (AUC), corresponding to a 40% increase in elimination half-life. This interaction was not evident with an MAO-B inhibitor.

A small study 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.

CLINICAL STUDIES

The efficacy of IMITREX Tablets in the acute treatment of migraine headaches was demonstrated in 3, randomized, double-blind, placebo-controlled studies. Patients enrolled in these 3 studies were predominately female (87%) and Caucasian (97%), with a mean age of 40 years (range, 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 Studies 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 studies. The frequency and time to use of these additional treatments were also determined. In all studies, doses of 25, 50, and 100 mg were compared to placebo in the treatment of migraine attacks. In 1 study, doses of 25, 50, and 100 mg were also compared to 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 to those who received placebo. In 1 of the 3 studies, there was a statistically significant greater percentage of patients with headache response at 2 and 4 hours in the 50- or 100-mg group when compared to the 25-mg dose groups. There were no statistically significant differences between the 50- and 100-mg dose groups in any study. The results from the 3 controlled clinical trials are summarized in Table 1.

Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.

IMITREX® (sumatriptan succinate) Tablets

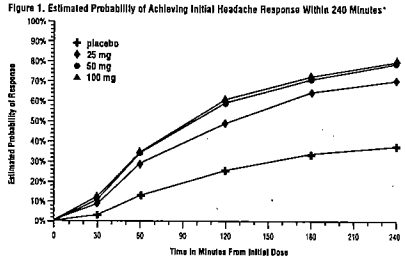
Table 1. Percentage of Patients With Headache Response (No or Mild Pain) 2 and 4 Hours Following Treatment

	Placebo		IMITREX Tablets 25 mg		IMITREX Tablets 50 mg		IMITREX Tablets 100 mg	
	2 hr	4 hr	2 hr	4 hr	2 hr	4 hr	2 hr	4 hr
Study 1	27% (n = 94)	38%	52%* (n = 298)	67%*	61%*† (n = 296)	78%*†	62%*† (n = 296)	79%*†
Study 2	26% (n = 65)	38%	52%* (n = 66)	70%*	50%* (n = 62)	68%*	56%* (n = 66)	71%*
Study 3	17% (n = 47)	19%	52%* (n = 48)	65%*	54%* (n = 46)	72%*	57%* (n = 46)	78%*

*$p<0.05$ in comparison with placebo.
†$p<0.05$ in comparison with 25 mg.

The estimated probability of achieving an initial headache response over the 4 hours following treatment is depicted in Figure 1.

Figure 1. Estimated Probability of Achieving Initial Headache Response Within 240 Minutes*

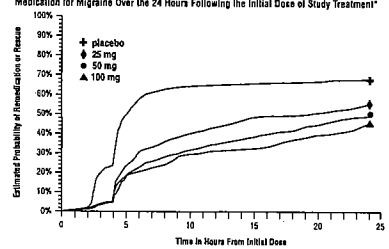


*The figure shows the probability over time of obtaining headache response (no or mild pain) following treatment with sumatriptan. The averages displayed are based on pooled data from the 3 clinical controlled trials providing evidence of efficacy. Kaplan-Meier plot with patients not achieving response 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 (Study 1) and at 4 hours (Studies 1, 2, and 3) following administration of IMITREX Tablets compared to placebo.

As early as 2 hours in Studies 2 and 3 or 4 hours in Study 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 or Other Medication for Migraine Over the 24 Hours Following the Initial Dose of Study Treatment*



*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.

IMITREX® (

There is evidence that doses above 50 mg do not provide a great
was associated with an increase in the severity of recurrent headache
prior to treatment; gender, age, or weight of the patient; relationship t
calcium channel blockers, tricyclic antidepressants). There were insu

INDICATIONS AND USAGE

IMITREX Tablets are indicated for the acute treatment of migraine
IMITREX Tablets are not intended for the prophylactic therapy of m
TIONS). Safety and effectiveness of IMITREX Tablets have not been e

CONTRAINDICATIONS

IMITREX Tablets should not be given to patients with history, sy
In addition, patients with other significant underlying cardiovasc
but are not limited to, angina pectoris of any type (e.g., stable an
of myocardial infarction, and silent myocardial ischemia. Cerebro
siemi ischemic attacks. Peripheral vascular disease includes, but
Because IMITREX Tablets may increase blood pressure, they sh
Concurrent administration of MAO-A inhibitors or use within 2
PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Inte
IMITREX Tablets should not be administered to patients with he
IMITREX Tablets and any ergotamine-containing or ergot-type m
each other, nor should IMITREX and another 5-HT_1 agonist.
IMITREX Tablets are contraindicated in patients with hypersensi
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WARNINGS

IMITREX Tablets should only be used where a clear diagnosis o
Risk of Myocardial Ischemia and/or Infarction and Other Adverse
vasospastic coronary artery disease (CAD) (see CONTRAINDICA
unrecognized CAD is predicted by the presence of risk factors (e.
of CAD, female with a surgical or physiological menopause, or mal
evidence that the patient is reasonably free of coronary artery and
sensitivity of cardiac diagnostic procedures to detect cardiovascu
the cardiovascular evaluation, the patient's medical history or ele
artery vasospasm or myocardial ischemia, sumatriptan should not
For patients with risk factors predictive of CAD, who are determin
istration of the first dose of sumatriptan tablets take place in the s
patient has previously received sumatriptan. Because cardiac ischem
on the first occasion of use an electrocardiogram (ECG) during the
It is recommended that patients who are intermittent long-term
above, undergo periodic interval cardiovascular evaluation as the
The systematic approach described above is intended to reduce
exposed to sumatriptan.
Drug-Associated Cardiac Events and Fatalities: Serious adverse c
rhythm, and death have been reported within a few hours following the
the extent of use of sumatriptan in patients with migraine, the incide
The fact that sumatriptan can cause coronary vasospasm, that so
documented absence of CAD, and the close proximity of the events t
In many cases, however, where there has been known underlying co
Premarketing Experience With Sumatriptan: Of 6,348 patients wh
sumatriptan, 2 experienced clinical adverse events shortly after recei
events was associated with a serious clinical outcome.
Among the more than 1,000 patients with migraine who participate
who sustained clinical events during or shortly after receiving suma
changes consistent with transient ischemia, but without accompanyi
risk factors predictive of CAD prior to study enrollment.
Among approximately 4,000 patients with migraine who participate
experienced an asymptomatic subendocardial infarction possibly sut
Postmarketing Experience With Sumatriptan: Serious cardiova
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of the reported cases that were actually caused by sumatriptan or to r
between the administration of IMITREX and the onset of the clinica
en events beginning within 1 hour of the administration of IMITREX.
Cardiac events that have been observed to have onset within 1 h
myocardial infarction, ventricular tachycardia and ventricular fibrillati
Some of these events occurred in patients who had no findings of
domestic reports of serious cardiac events within 1 hour of sumatrip
of significant underlying CAD was established in most cases (see CO
Drug-Associated Cerebrovascular Events and Fatalities: Cerebral h
reported in patients treated with oral or subcutaneous sumatriptan, ar
In a number of cases, it appears possible that the cerebrovascular ev
tions experienced were a consequence of migraine when they were
ously diagnosed as migraineurs, and in migraineurs who present wi
conditions. It should also be noted that patients with migraine may b
ischemic attack).
Other Vasospasm-Related Events: Sumatriptan may cause vasospa
colonic ischemia with abdominal pain and bloody diarrhea have been
Increase in Blood Pressure: Significant elevation in blood pressure, i
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IMITREX® (sumatriptan succinate) Tablets
PRESCRIBING INFORMATION 4153251

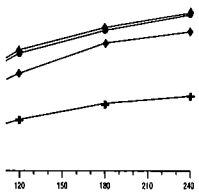
IMITREX® (sumatriptan succinate) Tablets

sponse (No or Mild Pain) 2 and 4 Hours Following Treatment

IMITREX Tablets 25 mg 2 hr	IMITREX Tablets 25 mg 4 hr	IMITREX Tablets 50 mg 2 hr	IMITREX Tablets 50 mg 4 hr	IMITREX Tablets 100 mg 2 hr	IMITREX Tablets 100 mg 4 hr
52%*	67%*	61%*†	78%*†	62%*†	79%*†
(n = 298)		(n = 296)		(n = 296)	
52%*	70%*	50%*	68%*	56%*	71%*
(n = 66)		(n = 62)		(n = 66)	
52%*	65%*	54%*	72%*	57%*	78%*
(n = 48)		(n = 46)		(n = 46)	

adache response over the 4 hours following treatment is depicted in Figure 1.

l Headache Response Within 240 Minutes*



otes From Initial Dose

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displayed are based on pooled data from the
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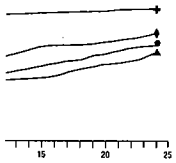

s From Initial Dose

ical controlled trials providing evidence of effi-
ssed to 24 hours. Plot also includes patients
tion was allowed within 2 hours postdose.

IMITREX® (sumatriptan succinate) Tablets

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 sumatriptan 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 patient; 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.

INDICATIONS AND USAGE

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

IMITREX Tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of IMITREX Tablets have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

IMITREX Tablets should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive IMITREX Tablets. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease (see WARNINGS).

Because IMITREX Tablets may increase blood pressure, they should not be given to patients with uncontrolled hypertension.

Concurrent administration of MAO-A inhibitors or use within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions).

IMITREX Tablets should not be administered to patients with hemiplegic or basilar migraine.

IMITREX Tablets and any ergotamine-containing or ergot-type medication (like dihydroergotamine or methysergide) should not be used within 24 hours of each other, nor should IMITREX and another 5-HT$_1$ agonist.

IMITREX Tablets are contraindicated in patients with hypersensitivity to sumatriptan or any of their components.

IMITREX Tablets are contraindicated in patients with severe hepatic impairment.

WARNINGS

IMITREX Tablets should only be used where a clear diagnosis of migraine headache has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: Sumatriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that sumatriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, sumatriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of sumatriptan tablets take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received sumatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following IMITREX Tablets, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of sumatriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use sumatriptan.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to sumatriptan.

Drug-Associated Cardiac Events and Fatalities: Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of IMITREX® (sumatriptan succinate) injection or IMITREX Tablets. Considering the extent of use of sumatriptan in patients with migraine, the incidence of these events is extremely low.

The fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying coronary artery disease, the relationship is uncertain.

Premarketing Experience With Sumatriptan: Of 6,348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral sumatriptan, 2 experienced clinical adverse events shortly after receiving oral sumatriptan that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.

Among the more than 1,900 patients with migraine who participated in premarketing controlled clinical trials of subcutaneous sumatriptan, there were 8 patients who sustained clinical events during or shortly after receiving sumatriptan that may have reflected coronary artery vasospasm. Six of these 8 patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these 8 patients, 4 had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.

Among approximately 4,000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of sumatriptan nasal spray, 1 patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.

Postmarketing Experience With Sumatriptan: Serious cardiovascular events, some resulting in death, have been reported in association with the use of IMITREX Injection or IMITREX Tablets. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by sumatriptan or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of IMITREX and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of IMITREX.

Cardiac events that have been observed to have onset within 1 hour of sumatriptan administration include: coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.

Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among domestic reports of serious cardiac events within 1 hour of sumatriptan administration, almost all of the patients had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).

Drug-Associated Cerebrovascular Events and Fatalities: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or subcutaneous sumatriptan, and some have resulted in fatalities. The relationship of sumatriptan to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, sumatriptan having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., cerebrovascular accident, transient ischemic attack).

Other Vasospasm-Related Events: Sumatriptan may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. Sumatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). Sumatriptan should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.

IMITREX® (sumatriptan succinate) Tablets

Concomitant Drug Use: In patients taking MAO-A inhibitors, sumatriptan plasma levels attained after treatment with recommended doses are 7-fold higher following oral administration than those obtained under other conditions. Accordingly, the coadministration of IMITREX Tablets and an MAO-A inhibitor is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

Hypersensitivity: Hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred on rare occasions in patients receiving sumatriptan. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS).

PRECAUTIONS

General: Chest discomfort and jaw or neck tightness have been reported following use of IMITREX Tablets and have also been reported infrequently following administration of IMITREX Nasal Spray. Chest, jaw, or neck tightness is relatively common after administration of IMITREX Injection. Only rarely have these symptoms been associated with ischemic ECG changes. However, because sumatriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following sumatriptan should be evaluated for the presence of CAD or a predisposition to Prinzmetal variant angina before receiving additional doses of sumatriptan, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud syndrome following sumatriptan should be evaluated for atherosclerosis or predisposition to vasospasm (see WARNINGS).

IMITREX should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic or renal function.

There have been rare reports of seizure following administration of sumatriptan. Sumatriptan should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache or who experience a headache that is atypical for them. There have been rare reports where patients received sumatriptan for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion (see WARNINGS).

For a given attack, if a patient does not respond to the first dose of sumatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

Binding to Melanin-Containing Tissues: In rats treated with a single subcutaneous dose (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or its metabolites bind to the melanin of the eye. Because there could be an accumulation in melanin-rich tissues over time, this raises the possibility that sumatriptan could cause toxicity in those tissues after extended use. However, no effects on the retina related to treatment with sumatriptan were noted in any of the oral or subcutaneous toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Corneal Opacities: Sumatriptan causes corneal opacities and defects in the corneal epithelium in dogs; this raises the possibility that these changes may occur in humans. While patients were not systematically evaluated for these changes in clinical trials, and no specific recommendations for monitoring are being offered, prescribers should be aware of the possibility of these changes (see ANIMAL TOXICOLOGY).

Information for Patients: See PATIENT INFORMATION at the end of this labeling for the text of the separate leaflet provided for patients.

Laboratory Tests: No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with sumatriptan.

Drug Interactions: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

MAO-A inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of IMITREX Tablets in patients receiving MAO-A inhibitors is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with sumatriptan. If concomitant treatment with sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

Drug/Laboratory Test Interactions: IMITREX Tablets are not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenesis:*** In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage (rats, 104 weeks) or drinking water (mice, 78 weeks). Average exposures achieved in mice receiving the highest dose (target dose of 160 mg/kg/day) were approximately 40 times the exposure attained in humans after the maximum recommended single oral dose of 100 mg. The highest dose administered to rats (160 mg/kg/day, reduced from 360 mg/kg/day during week 21) was approximately 15 times the maximum recommended single human oral dose of 100 mg on a mg/m^2 basis. There was no evidence of an increase in tumors in either species related to sumatriptan administration.

Mutagenesis: Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the in vitro mammalian Chinese hamster V79/HGPRT assay). In 2 cytogenetics assays (the in vitro human lymphocyte assay and the in vivo rat micronucleus assay) sumatriptan was not associated with clastogenic activity.

Impairment of Fertility: In a study in which male and female rats were dosed daily with oral sumatriptan 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 50 and 500 mg/kg/day. The highest no-effect dose for this finding was 5 mg/kg/day, or approximately one half of the maximum recommended single human oral dose of 100 mg on a mg/m^2 basis. It is not clear whether the problem is associated with treatment of the males or females or both combined. In a similar study by the subcutaneous route there was no evidence of impaired fertility at 60 mg/kg/day, the maximum dose tested, which is equivalent to approximately 6 times the maximum recommended single human oral dose of 100 mg on a mg/m^2 basis.

Pregnancy: Pregnancy Category C. In reproductive toxicity studies in rats and rabbits, oral treatment with sumatriptan was associated with embryolethality, fetal abnormalities, and pup mortality. When administered by the intravenous route to rabbits, sumatriptan has been shown to be embryolethal. There are no adequate and well-controlled studies in pregnant women. Therefore, IMITREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In assessing this information, the following findings should be considered.

Embryolethality: When given orally or intravenously to pregnant rabbits daily throughout the period of organogenesis, sumatriptan caused embryolethality at doses at or close to those producing maternal toxicity. In the oral studies this dose was 100 mg/kg/day, and in the intravenous studies this dose was 2.0 mg/kg/day. The mechanism of the embryolethality is not known. The highest no-effect dose for embryolethality by the oral route was 50 mg/kg/day, which is approximately 9 times the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis. By the intravenous route, the highest no-effect dose was 0.75 mg/kg/day, or approximately one tenth of the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis.

The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at 12.5 mg/kg/day, the maximum dose tested, did not cause embryolethality. This dose is equivalent to the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis. Additionally, in a study in rats given subcutaneous sumatriptan daily prior to and throughout pregnancy at 60 mg/kg/day, the maximum dose tested, there was no evidence of increased embryo/fetal lethality. This dose is equivalent to approximately 6 times the maximum recommended single human oral dose of 100 mg on a mg/m^2 basis.

Teratogenicity: Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in an increased incidence of blood vessel abnormalities (cervicothoracic and umbilical) at doses of approximately 250 mg/kg/day or higher. The highest no-effect dose was approximately 60 mg/kg/day, which is approximately 6 times the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis. Oral treatment of pregnant rabbits with sumatriptan during the period of organogenesis resulted in an increased incidence of cervicothoracic vascular and skeletal abnormalities. The highest no-effect dose for these effects was 15 mg/kg/day, or approximately 3 times the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis.

A study in which rats were dosed daily with oral sumatriptan prior to and throughout gestation demonstrated embryo/fetal toxicity (decreased body weight, decreased ossification, increased incidence of rib variations) and an increased incidence of a syndrome of malformations (short tail/short body and vertebral disorganization) at 500 mg/kg/day. The highest no-effect dose was 50 mg/kg/day, or approximately 5 times the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis. In a study in rats dosed daily with subcutaneous sumatriptan prior to and throughout pregnancy, at a dose of 60 mg/kg/day, the maximum dose tested, there was no evidence of teratogenicity. This dose is equivalent to approximately 6 times the maximum recommended single human oral dose of 100 mg on a mg/m^2 basis.

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Pup Deaths: Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in a decrease in pup survival between birth and postnatal day 4 at doses of approximately 250 mg/kg/day or higher. The highest no-effect dose for this effect was approximately 60 mg/kg/day, or 6 times the maximum single recommended human oral dose of 100 mg on a mg/m² basis.

Oral treatment of pregnant rats with sumatriptan from gestational day 17 through postnatal day 21 demonstrated a decrease in pup survival measured at postnatal days 2, 4, and 20 at the dose of 1,000 mg/kg/day. The highest no-effect dose for this finding was 100 mg/kg/day, approximately 10 times the maximum single recommended human oral dose of 100 mg on a mg/m² basis. In a similar study in rats by the subcutaneous route there was no increase in pup death at 81 mg/kg/day, the highest dose tested, which is equivalent to 8 times the maximum single recommended human oral dose of 100 mg on a mg/m² basis.

Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to IMITREX, GlaxoSmithKline maintains a Sumatriptan Pregnancy Registry. Physicians are encouraged to register patients by calling (800) 336-2176.

Nursing Mothers: Sumatriptan is excreted in human breast milk. Therefore, caution should be exercised when considering the administration of IMITREX Tablets to a nursing woman.

Pediatric Use: Safety and effectiveness of IMITREX Tablets in pediatric patients have not been established.

Completed placebo-controlled clinical trials evaluating oral sumatriptan (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age-dependent, with younger patients reporting events more commonly than older adolescents. Postmarketing experience includes a limited number of reports that describe pediatric patients who have experienced adverse events, some clinically serious, after use of subcutaneous sumatriptan and/or oral sumatriptan. These reports include events similar in nature to those reported rarely in adults. A myocardial infarct has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Since clinical data to determine the frequency of serious adverse events in pediatric patients who might receive injectable, oral, or intranasal sumatriptan are not presently available, the use of sumatriptan in patients aged younger than 18 years is not recommended.

Geriatric Use: The use of sumatriptan in elderly patients is not recommended because elderly patients are more likely to have decreased hepatic function, they are at higher risk for CAD, and blood pressure increases may be more pronounced in the elderly (see WARNINGS).

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following the use of IMITREX Injection or Tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Significant hypertensive episodes, including hypertensive crises, have been reported on rare occasions in patients with or without a history of hypertension (see WARNINGS).

Incidence in Controlled Clinical Trials: Table 2 lists adverse events that occurred in placebo-controlled clinical trials in patients who took at least 1 dose of study drug. Only events that occurred at a frequency of 2% or more in any group treated with IMITREX Tablets and were more frequent in that group than in the placebo group are included in Table 2. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Table 2. Treatment-Emergent Adverse Events Reported by at Least 2% of Patients in Controlled Migraine Trials*

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

*Events that occurred at a frequency of 2% or more in the group treated with IMITREX Tablets and that occurred more frequently in that group than the placebo group.

Other events that occurred in more than 1% of patients receiving IMITREX Tablets and at least as often on placebo included nausea and/or vomiting, migraine, headache, hyposalivation, dizziness, and drowsiness/sleepiness.

IMITREX Tablets are generally well tolerated. Across all doses, most adverse reactions were mild and transient and did not lead to long-lasting effects. The incidence of adverse events 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 events.

Other Events Observed in Association With the Administration of IMITREX Tablets: In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of IMITREX Tablets in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used IMITREX Tablets (25, 50, or 100 mg) and reported an event divided by the total number of patients (N = 6,348) exposed to IMITREX Tablets. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients, infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, and rare adverse events are those occurring in fewer than 1/1,000 patients.

Atypical Sensations: Frequent were burning sensation and numbness. Infrequent was tight feeling in head. Rare were dysesthesia.

Cardiovascular: Frequent were palpitations, syncope, decreased blood pressure, and increased blood pressure. Infrequent were arrhythmia, changes in ECG, hypertension, hypotension, pallor, pulsating sensations, and tachycardia. Rare were angina, atherosclerosis, bradycardia, cerebral ischemia, cerebrovascular lesion, heart block, peripheral cyanosis, thrombosis, transient myocardial ischemia, and vasodilation.

Ear, Nose, and Throat: Frequent were sinusitis, tinnitus; allergic rhinitis; upper respiratory inflammation; ear, nose, and throat hemorrhage; external otitis; hearing loss; nasal inflammation; and sensitivity to noise. Infrequent were hearing disturbances and otalgia. Rare was feeling of fullness in the ear(s).

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Endocrine and Metabolic: Infrequent was thirst. Rare were elevated thyrotropin stimulating hormone (TSH) levels; galactorrhea; hyperglycemia; hypoglycemia; hypothyroidism; polydipsia; weight gain; weight loss; endocrine cysts, lumps, and masses; and fluid disturbances.

Eye: Rare were disorders of sclera, mydriasis, blindness and low vision, visual disturbances, eye edema and swelling, eye irritation and itching, accommodation disorders, external ocular muscle disorders, eye hemorrhage, eye pain, and keratitis and conjunctivitis.

Gastrointestinal: Frequent were diarrhea and gastric symptoms. Infrequent were constipation, dysphagia, and gastroesophageal reflux. Rare were gastrointestinal bleeding, hematemesis, melena, peptic ulcer, gastrointestinal pain, dyspeptic symptoms, dental pain, feelings of gastrointestinal pressure, gastroesophageal reflux, gastritis, gastroenteritis, hypersalivation, abdominal distention, oral itching and irritation, salivary gland swelling, and swallowing disorders.

Hematological Disorders: Rare was anemia.

Musculoskeletal: Frequent was myalgia. Infrequent was muscle cramps. Rare were tetany; muscle atrophy, weakness, and tiredness; arthralgia and articular rheumatitis, acquired musculoskeletal deformity; muscle stiffness, tightness, and rigidity; and musculoskeletal inflammation.

Neurological: Frequent were phonophobia and photophobia. Infrequent were confusion, depression, difficulty concentrating, disturbance of smell, dysarthria, euphoria, facial pain, heat sensitivity, incoordination, facrimation, monoplegia, sleep disturbance, shivering, syncope, and tremor. Rare were aggressiveness, apathy, bradykinesia, cluster headache, convulsions, decreased appetite, drug abuse, dystonic reaction, facial paralysis, hallucinations, hunger, hyperesthesia, hysteria, increased alertness, memory disturbance, neuralgia, paralysis, personality change, phobia, radiculopathy, rigidity, suicide, twitching, agitation, anxiety, depressive disorders, detachment, motor dysfunction, neurotic disorders, psychomotor disorders, taste disturbances, and raised intracranial pressure.

Respiratory: Frequent was dyspnea. Infrequent was asthma. Rare were hiccoughs, breathing disorders, cough, and bronchitis.

Skin: Frequent was sweating. Infrequent were erythema, pruritus, rash, and skin tenderness. Rare were dry/scaly skin, tightness of skin, wrinkling of skin, eczema, seborrheic dermatitis, and skin nodules.

Breasts: Infrequent was tenderness. Rare were nipple discharge; breast swelling; cysts, lumps, and masses of breasts; and primary malignant breast neoplasm.

Urogenital: Infrequent were dysmenorrhea, increased urination, and intermenstrual bleeding. Rare were abortion and hematuria, urinary frequency, bladder inflammation, micturition disorders, urethritis, urinary infections, menstruation symptoms, abnormal menstrual cycle, inflammation of fallopian tubes, and menstrual cycle symptoms.

Miscellaneous: Frequent was hypersensitivity. Infrequent were fever, fluid retention, and overdose. Rare were edema, hematoma, lymphadenopathy, speech disturbance, voice disturbances, contusions.

Other Events Observed in the Clinical Development of IMITREX: The following adverse events occurred in clinical trials with IMITREX Injection and IMITREX Nasal Spray. Because the reports include events observed in open and uncontrolled studies, the role of IMITREX in their causation cannot be reliably determined. All reported events are included except those already listed, those too general to be informative, and those not reasonably associated with the use of the drug.

Atypical Sensations: Feeding struggle, prickling sensation, tingling, and hot sensation.

Cardiovascular: Abdominal aortic aneurysm, abnormal pulse, flushing, phlebitis, Raynaud syndrome, and various transient ECG changes (nonspecific ST or T wave changes, prolongation of PR or QTc intervals, sinus arrhythmia, nonsustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats, delayed activation of the right ventricle).

Chest Symptoms: Chest discomfort.

Endocrine and Metabolic: Dehydration.

Ear, Nose, and Throat: Disorder/discomfort nasal cavity and sinuses, ear infection, Meniere disease, and throat discomfort.

Eye: Vision alterations.

Gastrointestinal: Abdominal discomfort, colitis, disturbance of liver function tests, flatulence/eructation, gallstones, intestinal obstruction, pancreatitis, and retching.

Injection Site Reaction

Miscellaneous: Difficulty in walking, hypersensitivity to various agents, jaw discomfort, miscellaneous laboratory abnormalities, "serotonin agonist effect," swelling of the extremities, and swelling of the face.

Mouth and Teeth: Disorder of mouth and tongue (e.g., burning of tongue, numbness of tongue, dry mouth).

Musculoskeletal: Arthritis, backache, intervertebral disc disorder, neck pain/stiffness, need to flex calf muscles, and various joint disturbances (pain, stiffness, swelling, ache).

Neurological: Bad/unusual taste, chills, diplegia, disturbance of emotions, sedation, globus hysterious, intoxication, myoclonia, neoplasm of pituitary, relaxation, sensation of lightness, simultaneous hot and cold sensations, stinging sensations, stress, tickling sensations, transient hemiplegia, and yawning.

Respiratory: Influenza and diseases of the lower respiratory tract and lower respiratory tract infection.

Skin: Skin eruption, herpes, and peeling of the skin.

Urogenital: Disorder of breasts, endometriosis, and renal calculus.

Postmarketing Experience (Reports for Subcutaneous or Oral Sumatriptan): The following section enumerates potentially important adverse events that have occurred in clinical practice and that have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and nondomestic use of oral or subcutaneous dosage forms of sumatriptan. The events enumerated include all except those already listed in the ADVERSE REACTIONS section above or those too general to be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of sumatriptan in their causation cannot be reliably determined. It is assumed, however, that systemic reactions following sumatriptan use are likely to be similar regardless of route of administration.

Blood: Hemolytic anemia, pancytopenia, thrombocytopenia.

Cardiovascular: Atrial fibrillation, cardiomyopathy, colonic ischemia (see WARNINGS), Prinzmetal variant angina, pulmonary embolism, shock, thrombophlebitis.

Ear, Nose, and Throat: Deafness.

Eye: Ischemic optic neuropathy, retinal artery occlusion, retinal vein thrombosis, loss of vision.

Gastrointestinal: Ischemic colitis with rectal bleeding (see WARNINGS), xerostomia.

Hepatic: Elevated liver function tests.

Neurological: Central nervous system vasculitis, cerebrovascular accident, dysphasia, subarachnoid hemorrhage.

Non-Site Specific: Angioneurotic edema, cyanosis, death (see WARNINGS), temporal arteritis.

Psychiatry: Panic disorder.

Respiratory: Bronchospasm in patients with and without a history of asthma.

Skin: Exacerbation of sunburn, hypersensitivity reactions (allergic vasculitis, erythema, pruritus, rash, shortness of breath, urticaria; in addition, severe anaphylaxis/anaphylactoid reactions have been reported (see WARNINGS)), photosensitivity.

Urogenital: Acute renal failure.

DRUG ABUSE AND DEPENDENCE

One clinical study with IMITREX® (sumatriptan succinate) injection enrolling 12 patients with a history of substance abuse failed to induce subjective behavior and/or physiologic response ordinarily associated with drugs that have an established potential for abuse.

OVERDOSAGE

Patients (N = 670) have received single oral doses of 140 to 300 mg without significant adverse effects. Volunteers (N = 174) have received single oral doses of 140 to 400 mg without serious adverse events.

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), 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.

IMITREX® (sumatriptan succinate) Tablets

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 25, 50, or 100 mg of IMITREX Tablets were effective for the acute treatment of migraine in adults. There l that doses of 50 and 100 mg may provide a greater effect than 25 mg (see CLINICAL TRIALS). There is also evidence that doses of 100 mg do not provic effect than 50 mg. Individuals may vary in response to doses of IMITREX Tablets. The choice of dose should therefore be made on an individual basis the possible benefit of a higher dose with the potential for a greater risk of adverse events.

If the headache returns or the patient has a partial response to the initial dose, the dose may be repeated after 2 hours, not to exceed a total daily dose If a headache returns following an initial treatment with IMITREX Injection, additional single IMITREX Tablets (up to 100 mg/day) may be given with an 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.

Because of the potential of MAO-A inhibitors to cause unpredictable elevations in the bioavailability of oral sumatriptan, their combined use is contr (see CONTRAINDICATIONS).

Hepatic disease/functional impairment may also cause unpredictable elevations in the bioavailability of orally administered sumatriptan. Consequently, I is deemed advisable in the presence of liver disease, the maximum single dose should in general not exceed 50 mg (see CLINICAL PHARMACOLOGY f of this recommendation).

HOW SUPPLIED

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

IMITREX Tablets, 25 mg are white, triangular-shaped, film-coated tablets debossed with "1" 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 oth 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 ot ter packs of 9 tablets (NDC 0173-0737-01).

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

ANIMAL TOXICOLOGY

Corneal Opacities: Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at dosage 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 exa for these toxicities were not conducted and no-effect doses were not established; however, the relative exposure at the lowest dose tested was approximat the human exposure after a 100-mg oral dose. There is evidence of alterations in corneal appearance on the first day of intranasal dosing to dogs. Cha noted at the lowest dose tested, which was approximately one half the maximum single human oral dose of 100 mg on a mg/m² basis.

PATIENT INFORMATION

The following wording is contained in a separate leaflet provided for patients.

Information for the Patient
IMITREX® (sumatriptan succinate) Tablets

Please read this leaflet carefully before you take IMITREX Tablets. This provides a summary of the information available on your medicine. Please do not t this leaflet until you have finished your medicine. You may need to read this leaflet again. This leaflet does not contain all the information on IMITREX ' further information or advice, ask your doctor or pharmacist.

Information About Your Medicine:

The name of your medicine is IMITREX (sumatriptan succinate) Tablets. It can be obtained only by prescription from your doctor. The decision to us Tablets is one that you and your doctor should make jointly, taking into account your individual preferences and medical circumstances. If you have a for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmer or a male over 40 years of age), you should tell your doctor, who should evaluate you for heart disease in order to determine if IMITREX is appropriate for Although the vast majority of those who have taken IMITREX have not experienced any significant side effects, some individuals have experienced seri problems and, rarely, considering the extensiveness of IMITREX use worldwide, deaths have been reported. In all but a few instances, however, serious occurred in people with known heart disease and it was not clear whether IMITREX was a contributory factor in these deaths.

1. The Purpose of Your Medicine:

IMITREX Tablets are intended to relieve your migraine, but not to prevent or reduce the number of attacks you experience. Use IMITREX Tablets onl an actual migraine attack.

2. Important Questions to Consider Before Taking IMITREX Tablets:

If the answer to any of the following questions is YES or if you do not know the answer, then please discuss it with your doctor before you use IMITR

- Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Are you using inadequate contraception? Are you bre
- Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have you had a heart attack?
- Do you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart you are postmenopausal or a male over 40 years of age)?
- Have you had a stroke, transient ischemic attacks (TIAs), or Raynaud syndrome?
- Do you have high blood pressure?
- Have you ever had to stop taking this or any other medicine because of an allergy or other problems?
- Are you taking any other migraine medicines, including other 5-HT$_1$ agonists or any other medicines containing ergotamine, dihydroergotamine, or meth
- Are you taking any medicine for depression (monoamine oxidase inhibitors or selective serotonin reuptake inhibitors [SSRIs])?
- Have you had, or do you have, any disease of the liver or kidney?
- Have you had, or do you have, epilepsy or seizures?
- Is this headache different from your usual migraine attacks?

Remember, if you answered YES to any of the above questions, then discuss it with your doctor.

3. The Use of IMITREX Tablets During Pregnancy:

Do not use IMITREX Tablets if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contracept you have discussed this with your doctor.

4. How to Use IMITREX Tablets:

For adults, the usual dose is a single tablet taken whole with fluids. A second tablet may be taken if your symptoms of migraine come back or if you h tial response to the initial dose, but not sooner than 2 hours following the first tablet. For a given attack, if you have no response to the first tablet, do not second tablet without first consulting with your doctor. Do not take more than a total of 200 mg of IMITREX Tablets in any 24-hour period. The safety of t average of more than 4 headaches in a 30-day period has not been established.

5. Side Effects to Watch for:

- Some patients experience pain or tightness in the chest or throat when using IMITREX Tablets. If this happens to you, then discuss it with your doc using any more IMITREX Tablets. If the chest pain is severe or does not go away, call your doctor immediately.
- If you have sudden and/or severe abdominal pain following IMITREX Tablets, call your doctor immediately.
- Shortness of breath; wheezing; heart throbbing; swelling of eyelids, face, or lips; or a skin rash, skin lumps, or hives happens rarely. If it happens b tell your doctor immediately. Do not take any more IMITREX Tablets unless your doctor tells you to do so.
- Some people may have feelings of tingling, heat, flushing (redness of face lasting a short time), heaviness or pressure after treatment with IMITREX few people may feel drowsy, dizzy, tired, or sick. Tell your doctor if these symptoms at your next visit.

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esthesia, hysteria, increased
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, wrinkling of skin, eczema,

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urinary frequency, bladder
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REX Injection and IMITREX
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IMITREX® (sumatriptan succinate) Tablets

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 25, 50, or 100 mg of IMITREX Tablets were effective for the acute treatment of migraine in adults. There is evidence that doses of 50 and 100 mg may provide a greater effect than 25 mg (see CLINICAL TRIALS). There is also evidence that doses of 100 mg do not provide a greater effect than 50 mg. Individuals may vary in response to doses of IMITREX Tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of a higher dose with the potential for a greater risk of adverse events.

If the headache returns or the patient has a partial response to the initial dose, the dose may be repeated after 2 hours, not to exceed a total daily dose of 200 mg. If a headache returns following an initial treatment with IMITREX 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.

Because of the potential of MAO-A inhibitors to cause unpredictable elevations in the bioavailability of oral sumatriptan, their combined use is contraindicated (see CONTRAINDICATIONS).

Hepatic disease/functional impairment may also cause unpredictable elevations in the bioavailability of orally administered sumatriptan. Consequently, if treatment is deemed advisable in the presence of liver disease, the maximum single dose should in general not exceed 50 mg (see CLINICAL PHARMACOLOGY for the basis of this recommendation).

HOW SUPPLIED

IMITREX Tablets, 25, 50, 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 36° and 86°F (2° and 30°C).

ANIMAL TOXICOLOGY

Corneal Opacities: Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 69-week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established; however, the relative exposure at the lowest dose tested was approximately 5 times the human exposure after a 100-mg oral dose. There is evidence of alterations in corneal appearance on the first day of intranasal dosing to dogs. Changes were noted at the lowest dose tested, which was approximately one half the maximum single human oral dose of 100 mg on a mg/m² basis.

PATIENT INFORMATION

The following wording is contained in a separate leaflet provided for patients.

Information for the Patient
IMITREX® (sumatriptan succinate) Tablets

Please read this leaflet carefully before you take IMITREX Tablets. This provides a summary of the information available on your medicine. Please do not throw away this leaflet until you have finished your medicine. You may need to read this leaflet again. This leaflet does not contain all the information on IMITREX Tablets. For further information or advice, ask your doctor or pharmacist.

Information About Your Medicine:

The name of your medicine is IMITREX (sumatriptan succinate) Tablets. It can be obtained only by prescription from your doctor. The decision to use IMITREX Tablets is one that you and your doctor should make jointly, taking into account your individual preferences and medical circumstances. If you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40 years of age), you should tell your doctor, who should evaluate you for heart disease in order to determine if IMITREX is appropriate for you. Although the vast majority of those who have taken IMITREX have not experienced any significant side effects, some individuals have experienced serious heart problems and, rarely, considering the extensiveness of IMITREX use worldwide, deaths have been reported. In all but a few instances, however, serious problems occurred in people with known heart disease and it was not clear whether IMITREX was a contributory factor in these deaths.

1. The Purpose of Your Medicine:

IMITREX Tablets are intended to relieve your migraine, but not to prevent or reduce the number of attacks you experience. Use IMITREX Tablets only to treat an actual migraine attack.

2. Important Questions to Consider Before Taking IMITREX Tablets:

If the answer to any of the following questions is YES or if you do not know the answer, then please discuss it with your doctor before you use IMITREX Tablets.

- Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Are you using inadequate contraception? Are you breastfeeding?
- Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have you had a heart attack?
- Do you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40 years of age)?
- Have you had a stroke, transient ischemic attacks (TIAs), or Raynaud syndrome?
- Do you have high blood pressure?
- Have you ever had to stop taking this or any other medicine because of an allergy or other problems?
- Are you taking any other migraine medicines, including other 5-HT_1 agonists or any other medicines containing ergotamine, dihydroergotamine, or methysergide?
- Are you taking any medicine for depression (monoamine oxidase inhibitors or selective serotonin reuptake inhibitors [SSRIs])?
- Have you had, or do you have, any disease of the liver or kidney?
- Have you had, or do you have, epilepsy or seizures?
- Is this headache different from your usual migraine attacks?

Remember, if you answered YES to any of the above questions, then discuss it with your doctor.

3. The Use of IMITREX Tablets During Pregnancy:

Do not use IMITREX Tablets if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contraception, unless you have discussed this with your doctor.

4. How to Use IMITREX Tablets:

For adults, the usual dose is a single tablet taken whole with fluids. A second tablet may be taken if your symptoms of migraine come back or if you have a partial response to the initial dose, but not sooner than 2 hours following the first tablet. For a given attack, if you have no response to the first tablet, do not take a second tablet without first consulting with your doctor. Do not take more than a total of 200 mg of IMITREX Tablets in any 24-hour period. The safety of treating an average of more than 4 headaches in a 30-day period has not been established.

5. Side Effects to Watch for:

- Some patients experience pain or tightness in the chest or throat when using IMITREX Tablets. If this happens to you, then discuss it with your doctor before using any more IMITREX Tablets. If the chest pain is severe or does not go away, call your doctor immediately.
- If you have sudden and/or severe abdominal pain following IMITREX Tablets, call your doctor immediately.
- Shortness of breath; wheeziness; heart throbbing; swelling of eyelids, face, or lips; or a skin rash, skin lumps, or hives happens rarely. If it happens to you, then tell your doctor immediately. Do not take any more IMITREX Tablets unless your doctor tells you to do so.
- Some people may have feelings of tingling, heat, flushing (redness of face lasting a short time), heaviness or pressure after treatment with IMITREX Tablets. A few people may feel drowsy, dizzy, tired, or sick. Tell your doctor of these symptoms at your next visit.

IMITREX® (sumatriptan succinate) Tablets

- If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your doctor immediately.

6. What to Do if an Overdose Is Taken:

If you have taken more medicine than you have been told, contact either your doctor, hospital emergency department, or nearest poison control center immediately.

7. Storing Your Medicine:

Keep your medicine in a safe place where children cannot reach it. It may be harmful to children. Store your medicine away from heat and light. Do not store at temperatures above 86°F (30°C), or below 36°F (2°C). If your medicine has expired (the expiration date is printed on the treatment pack), throw it away as instructed. If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.

GlaxoSmithKline

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