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: Among 3,653 patients treated with IMITREX Nasal Spray in active- and placebo-controlled clinical trials, less than 0.4% of patients withdrew for reasons related to adverse events. Table 2 lists adverse events that occurred in worldwide placebo-controlled clinical trials in 3,419 migraineurs. 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.

Only events that occurred at a frequency of 1% or more in the IMITREX Nasal Spray 20-mg treatment group and were more frequent in that group than in the placebo group are included in Table 2.

[See table above]

Phonophobia also occurred in more than 1% of patients but was more frequent on placebo.

IMITREX Nasal Spray is 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, 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 events.

Other Events Observed in Association With the Administration of IMITREX Nasal Spray: 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 Nasal Spray 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 the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used IMITREX Nasal Spray (5, 10, or 20 mg in controlled and uncontrolled trials) and reported an event divided by the total number of patients (n = 3,711) exposed to IMITREX Nasal Spray. 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: 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: Infrequent were tingling, warm/hot sensation, numbness, pressure sensation, feeling strange, feeling of heaviness, feeling of tightness, paresthesia, cold sensation, and tight feeling in head. Rare were dysesthesia and prickling sensation.

Cardiovascular: Infrequent were flushing and hypertension (see WARNINGS), palpitations, tachycardia, changes in ECG, and arrhythmia (see WARNINGS and PRECAUTIONS). Rare were abdominal aortic aneurysm, hypotension, bradycardia, pallor, and phlebitis.

Chest Symptoms: Infrequent were chest tightness, chest discomfort, and chest pressure/heaviness (see PRECAUTIONS: General).

Ear, Nose, and Throat: Infrequent were disturbance of hearing and ear infection. Rare were otalgia and Meniere disease.

Endocrine and Metabolic: Infrequent was thirst. Rare were galactorrhea, hypothyroidism, and weight loss.

Eye: Infrequent were irritation of eyes and visual disturbance.

Gastrointestinal: Infrequent were abdominal discomfort, diarrhea, dysphagia, and gastroesophageal reflux. Rare were constipation, flatulence/eructation, hematemesis, intestinal obstruction, melena, gastroenteritis, colitis, hemorrhage of gastrointestinal tract, and pancreatitis.

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

Musculoskeletal: Infrequent were neck pain/stiffness, backache, weakness, joint symptoms, arthritis, and myalgia. Rare were muscle cramps, tetany, intervertebral disc disorder, and muscle stiffness.

Neurological: Infrequent were drowsiness/sedation, anxiety, sleep disturbances, tremors, syncope, shivers, chills, depression, agitation, sensation of lightness, and mental confusion. Rare were difficulty concentrating, hunger, lacrimation, memory disturbances, monoplegia/diplegia, apathy, disturbance of smell, disturbance of emotions, dysarthria, facial pain, intoxication, stress, decreased appetite, difficulty coordinating, euphoria, and neoplasm of pituitary.

Respiratory: Infrequent were dyspnea and lower respiratory tract infection. Rare was asthma.

Skin: Infrequent were rash/skin eruption, pruritus, and erythema. Rare were herpes, swelling of face, sweating, and peeling of skin.

Urogenital: Infrequent were dysuria, disorder of breasts, and dysmenorrhea. Rare were endometriosis and increased urination.

Miscellaneous: Infrequent were cough, edema, and fever. Rare were hypersensitivity, swelling of extremities, voice disturbances, difficulty in walking, and lymphadenopathy.

Other Events Observed in the Clinical Development of IMITREX: The following adverse events occurred in clinical trials with IMITREX Injection and IMITREX Tablets. 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.

Breasts: Breast swelling; cysts, lumps, and masses of breasts; nipple discharge; primary malignant breast neoplasm; and tenderness.

Cardiovascular: Abnormal pulse, angina, atherosclerosis, cerebral ischemia, cerebrovascular lesion, heart block, peripheral cyanosis, pulsating sensations, Raynaud syndrome, thrombosis, transient myocardial ischemia, 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), and vasodilation.

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

Endocrine and Metabolic: Dehydration; endocrine cysts, lumps, and masses; elevated thyrotropin stimulating hormone (TSH) levels; fluid disturbances; hyperglycemia; hypoglycemia; polydipsia; and weight gain.

Eye: Accommodation disorders, blindness and low vision, conjunctivitis, disorders of sclera, external ocular muscle disorders, eye edema and swelling, eye itching, eye hemorrhage, eye pain, keratitis, mydriasis, and vision alterations.

Gastrointestinal: Abdominal distention, dental pain, disturbances of liver function tests, dyspeptic symptoms, feelings of gastrointestinal pressure, gallstones, gastric symptoms, gastritis, gastrointestinal pain, hypersalivation, hyposalivation, oral itching and irritation, peptic ulcer, retching, salivary gland swelling, and swallowing disorders.

Hematological Disorders: Anemia.

Injection Site Reaction

Miscellaneous: Contusions, fluid retention, hematoma, hypersensitivity to various agents, jaw discomfort, miscellaneous laboratory abnormalities, overdose, "serotonin agonist effect", and speech disturbance.

Musculoskeletal: Acquired musculoskeletal deformity, arthralgia and articular rheumatitis, muscle atrophy, muscle tiredness, musculoskeletal inflammation, need to flex calf muscles, rigidity, tightness, and various joint disturbances (pain, stiffness, swelling, ache).

Neurological: Aggressiveness, bradylogia, cluster headache, convulsions, detachment, disturbances of taste, drug abuse, dystonia, facial paralysis, globus hystericus, hallucinations, headache, heat sensitivity, hyperesthesia, hysteria, increased alertness, malaise/fatigue, migraine, motor dysfunction, myoclonia, neuralgia, neurotic disorders, paralysis, personality change, phobia, photophobia, psychomotor disorders, radiculopathy, raised intracranial pressure, relaxation, stinging sensations, transient hemiplegia, simultaneous hot and cold sensations, suicide, tickling sensations, twitching, and yawning.

Pain and Other Pressure Sensations: Chest pain, neck tightness/pressure, throat/jaw pain/tightness/pressure, and pain (location specified).

Respiratory: Breathing disorders, bronchitis, diseases of the lower respiratory tract, hiccoughs, and influenza.

Skin: Dry/scaly skin, eczema, seborrheic dermatitis, skin nodules, skin tenderness, tightness of skin, and wrinkling of skin.

Urogenital: Abortion, abnormal menstrual cycle, bladder inflammation, hematuria, inflammation of fallopian tubes, intermenstrual bleeding, menstruation symptoms, micturition disorders, renal calculus, urethritis, urinary frequency, and urinary infections.

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.

Table 2. Treatment-Emergent Adverse Events Reported by at Least 1% of Patients in Controlled Migraine Trials

	Percent of Patients Reporting			
Adverse Event Type	Placebo (n = 704)	IMITREX 5 mg (n = 496)	IMITREX 10 mg (n = 1007)	IMITREX 20 mg (n = 1212)
Atypical sensations				
Burning sensation	0.1%	0.4%	0.6%	1.4%
Ear, nose, and throat				
Disorder/discomfort of nasal cavity/sinuses	2.4%	2.8%	2.5%	3.8%
Throat discomfort	0.9%	0.8%	1.8%	2.4%
Gastrointestinal				
Nausea and/or vomiting	11.3%	12.2%	11.0%	13.5%
Neurological				
Bad/unusual taste	1.7%	13.5%	19.3%	24.5%
Dizziness/vertigo	0.9%	1.0%	1.7%	1.4%

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

In clinical trials, the highest single doses of IMITREX Nasal Spray administered without significant adverse effects were 40 mg to 12 volunteers and 40 mg to 85 migraine patients, 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 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 about 2 hours (see CLINICAL PHARMACOLOGY), 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.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 5, 10, or 20 mg of IMITREX Nasal Spray administered into 1 nostril were effective for the acute treatment of migraine in adults. A greater proportion of patients had headache response following a 20-mg dose than following a 5- or 10-mg dose (see CLINICAL TRIALS). Individuals may vary in response to doses of IMITREX Nasal Spray. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 20-mg dose with the potential for a greater risk of adverse events. A 10-mg dose may be achieved by the administration of a single 5-mg dose in each nostril. There is evidence that doses above 20 mg do not provide a greater effect than 20 mg.

Continued on next page

This product information is based on labeling in effect on August 1, 2002. Further information is available at: GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709. 1-888-825-5249. Corporate Web Site: www.gsk.com

Imitrex Nasal Spray—Cont.

If the headache returns, the dose may be repeated once after 2 hours, not to exceed a total daily dose of 40 mg. The safety of treating an average of more than 4 headaches in a 30-day period has not been established.

HOW SUPPLIED

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 and 20 mg, respectively, of sumatriptan.

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

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 per day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established; however, the relative exposure at the lowest dose tested was approximately 5 times the human exposure after a 100-mg oral dose or 3 times the human exposure after a 6-mg subcutaneous dose or 22 times the human exposure after a single 20-mg intranasal 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 2 times the maximum single human intranasal dose of 20 mg on a mg/m^2 basis.

PATIENT INFORMATION

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

Information for the Patient
IMITREX® (sumatriptan) Nasal Spray

Please read this leaflet carefully before you administer IMITREX Nasal Spray. 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 Nasal Spray. For further information or advice, ask your doctor or pharmacist.

Information About Your Medicine:

The name of your medicine is IMITREX (sumatriptan) Nasal Spray. It can be obtained only by prescription from your doctor. The decision to use IMITREX Nasal Spray 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), 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 extensive use of IMITREX 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 Nasal Spray is intended to relieve your migraine, but not to prevent or reduce the number of attacks you experience. Use IMITREX Nasal Spray only to treat an actual migraine attack.

2. Important Questions to Consider Before Using IMITREX Nasal Spray:

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 Nasal Spray.

- 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)?
- 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 Nasal Spray During Pregnancy:

Do not use IMITREX Nasal Spray 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 Nasal Spray:

Before using IMITREX Nasal Spray, see the instruction pamphlet accompanying the product. For adults, the usual dose is a single nasal spray administered into 1 nostril. If your headache comes back, a second nasal spray may be administered anytime after 2 hours of administering the first spray. For any attack where you have no response to the first nasal spray, do not take a second nasal spray without first consulting with your doctor. Do not administer more than a total of 40 mg of IMITREX Nasal Spray in any 24-hour period. The effects of long-term repeated use of IMITREX Nasal Spray on the surfaces of the nose and throat have not been specifically studied. 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 Nasal Spray. If this happens to you, then discuss it with your doctor before using any more IMITREX Nasal Spray. 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 Nasal Spray, 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 Nasal Spray 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 Nasal Spray. A few people may feel drowsy, dizzy, tired, sick, or may experience nasal irritation. Tell your doctor of these symptoms at your next visit.
- 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 medicines 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 medicines 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, Research Triangle Park, NC 27709

April 2002/RL-1005

Shown in Product Identification Guide, page 316

IMITREX® Rx
[Im 'I-trĕx "]
(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).

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, iron oxide (100-mg tablet only), lactose, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

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_{5A}, and 5-HT_7 receptors and no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT_2, 5-HT_3, or 5-HT_4 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, 7-47 ng/mL) and 51 ng/mL (range, 28-100 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, 49-110 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). Food has no significant effect on the bioavailability of sumatriptan, but delays the t_{max} slightly (by about 0.5 hours).

Plasma protein binding is low (14%-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 (MAOI):*** 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 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, 18-65 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. Associ-

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Holdings ID	22487151730002122
	View all holdings
Barcode	89112334917
Item ID	23487151030002122
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Barcode	**89112334917**
Copy ID	**1**
Material type	**Issue**
Item policy	**general (book)**
Provenance	
Is magnetic	**No**
PO Line	Select from a list
Issue date	
Receiving date	**04/03/2003**
Expected receiving date	
Enumeration A	**2003**
Enumeration B	
Chronology I	

Declaration of Rachel J. Watters on Authentication of Publication

1. I, Rachel J. Watters, am a librarian, and the Director of Wisconsin TechSearch ("WTS"), located at 728 State Street, Madison, Wisconsin, 53706. WTS is an interlibrary loan department at the University of Wisconsin-Madison. I have worked as a librarian at the University of Wisconsin library system since 1998. I have been employed at WTS since 2002, first as a librarian and, beginning in 2011, as the Director. Through the course of my employment, I have become well informed about the operations of the University of Wisconsin library system, which follows standard library practices.

2. This Declaration relates to the dates of receipt and availability of the following:

Anonymous. (2010) Zomig Nasal Spray. *Physicians' Desk Reference*, pp. 768-778. Montvale, NJ: PDR Network.

3. *Standard operating procedures for materials at the University of Wisconsin-Madison Libraries*. When a volume was received by the Library, it would be checked in, stamped with the date of receipt, added to library holdings records, and made available to readers as soon after its arrival as possible. The procedure normally took a few days or at most 2 to 3 weeks.

4. Exhibit A to this Declaration is true and accurate copy of the front matter of the *Physicians' Desk Reference* (2010) publication, which includes a stamp showing that this book is the property of Ebling Library at the University of Wisconsin-Madison.

Exhibit A also includes an excerpt of pages 768 to 778 of that volume, showing the entry entitled *Zomig Nasal Spray* (2010).

5. Attached as Exhibit B is the cataloging system record of the University of Wisconsin-Madison Libraries for its copy of the *Zomig Nasal Spray* (2010) publication. As shown in the "Receiving date" field of this Exhibit, the University of Wisconsin-Madison Libraries owned this book and had it cataloged in the system as of June 4, 2010.

6. Members of the interested public could locate the *Zomig Nasal Spray* (2010) publication after it was cataloged by searching the public library catalog or requesting a search through WTS. The search could be done by title, author, and/or subject key words. Members of the interested public could access the publication by locating it on the library's shelves or requesting it from WTS.

7. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date: December 13, 2018

Wisconsin TechSearch

Rachel J. Watters
Director

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API

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Build custom dashboards for your attorneys and clients with live data direct from the court.

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Sync your system to PACER to automate legal marketing.