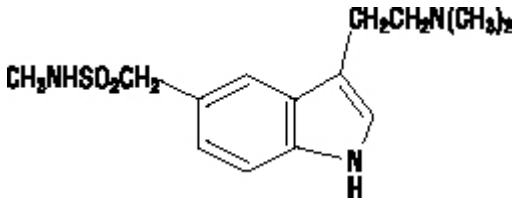
PRESCRIBING INFORMATION

IMITREX®
(sumatriptan)
Nasal Spray

DESCRIPTION

IMITREX (sumatriptan) Nasal Spray contains sumatriptan, a selective 5-hydroxytryptamine$_1$ receptor subtype agonist. Sumatriptan is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulfonamide, and it has the following structure:



The empirical formula is $C_{14}H_{21}N_3O_2S$, representing a molecular weight of 295.4. Sumatriptan is a white to off-white powder that is readily soluble in water and in saline. Each IMITREX Nasal Spray contains 5 or 20 mg of sumatriptan in a 100-µL unit dose aqueous buffered solution containing monobasic potassium phosphate NF, anhydrous dibasic sodium phosphate USP, sulfuric acid NF, sodium hydroxide NF, and purified water USP. The pH of the solution is approximately 5.5. The osmolality of the solution is 372 or 742 mOsmol for the 5- and 20-mg IMITREX Nasal Spray, respectively.

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

Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL, is low, approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated, but would be expected to be minor, given the low rate of protein binding. The mean volume of distribution after subcutaneous dosing is 2.7 L/kg and the total plasma clearance is approximately 1,200 mL/min.

The elimination half-life of sumatriptan administered as a nasal spray is approximately 2 hours, similar to the half-life seen after subcutaneous injection. Only 3% of the dose is excreted in the urine as unchanged sumatriptan; 42% of the dose is excreted as the major metabolite, the indole acetic acid analogue of sumatriptan.

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

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 effect of hepatic disease on the pharmacokinetics of subcutaneously and orally administered sumatriptan has been evaluated, but the intranasal dosage form has not been studied in hepatic impairment. There were no statistically significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in hepatically impaired patients compared to healthy controls. However, the liver plays an important role in the presystemic clearance of orally administered sumatriptan. In 1 small study involving oral sumatriptan in 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. The bioavailability of nasally absorbed sumatriptan following intranasal administration, which would not undergo first-pass metabolism, should not be altered in hepatically impaired patients. The bioavailability of the swallowed portion of the intranasal sumatriptan dose has not been determined, but would be increased in these patients. The swallowed intranasal dose is small, however, compared to the usual oral dose, so that its impact should be minimal.

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). Intranasal sumatriptan has not been evaluated for age differences (see PRECAUTIONS: Geriatric Use).

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

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

MAOI interaction studies have not been performed with intranasal sumatriptan. 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. The effects of an MAOI on systemic exposure after intranasal sumatriptan would be expected to be greater than the effect after subcutaneous sumatriptan but smaller than the effect after oral sumatriptan because only swallowed drug would be subject to first-pass effects.

In a 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.

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

CLINICAL TRIALS

The efficacy of IMITREX Nasal Spray in the acute treatment of migraine headaches was demonstrated in 8, randomized, double-blind, placebo-controlled studies, of which 5 used the recommended dosing regimen and used the marketed formulation. Patients enrolled in these 5 studies were predominately female (86%) and Caucasian (95%), with a mean age of 41 (range of 18 to 65). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed up to 2 hours after dosing. Associated symptoms such as nausea, photophobia, and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours postdose. A second dose of IMITREX Nasal Spray or other medication was allowed 2 to 24 hours after the initial treatment for recurrent headache. The frequency and time to use of these additional treatments were also determined. In all studies, doses of 10 and 20 mg were compared

to placebo in the treatment of 1 to 3 migraine attacks. Patients received doses as a single spray into 1 nostril. In 2 studies, a 5-mg dose was also evaluated.

In all 5 trials utilizing the market formulation and recommended dosage regimen, the percentage of patients achieving headache response 2 hours after treatment was significantly greater among patients receiving IMITREX Nasal Spray at all doses (with one exception) compared to those who received placebo. In 4 of the 5 studies, there was a statistically significant greater percentage of patients with headache response at 2 hours in the 20-mg group when compared to the lower dose groups (5 and 10 mg). There were no statistically significant differences between the 5- and 10-mg dose groups in any study. The results from the 5 controlled clinical trials are summarized in Table 1. Note that, in general, comparisons of results obtained in studies conducted under different conditions by different investigators with different samples of patients are ordinarily unreliable for purposes of quantitative comparison.

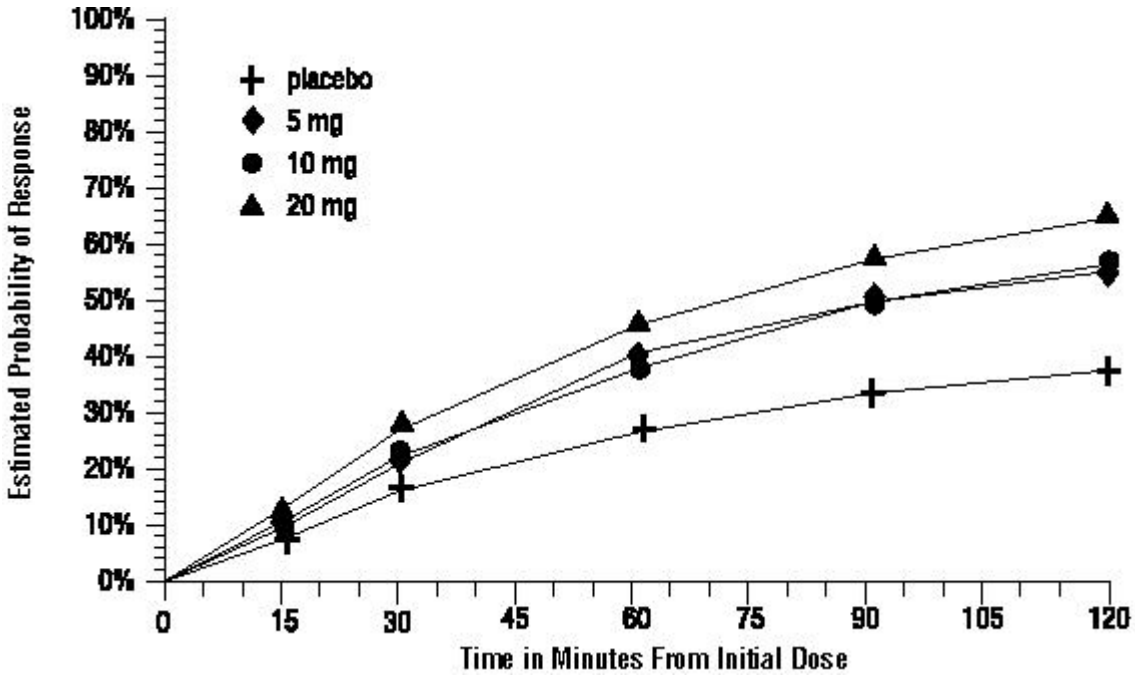
Table 1. Percentage of Patients With Headache Response (No or Mild Pain) 2 Hours Following Treatment

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

[a]$p<0.05$ in comparison with placebo.
[b]$p<0.05$ in comparison with 10 mg.
[c]$p<0.05$ in comparison with 5 mg.
[d]Data are for attack 1 only of multiattack study for comparison.

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

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



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

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

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

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