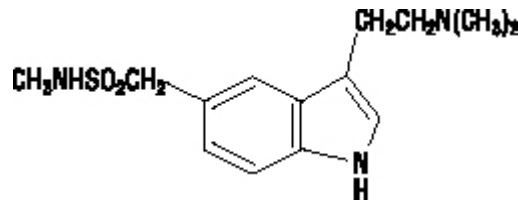


1 **PRESCRIBING INFORMATION**

2 **IMITREX<sup>®</sup>**  
3 **(sumatriptan)**  
4 **Nasal Spray**  
5

6 **DESCRIPTION**

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



11  
12  
13 The empirical formula is C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>S, representing a molecular weight of 295.4.  
14 Sumatriptan is a white to off-white powder that is readily soluble in water and in saline. Each  
15 IMITREX Nasal Spray contains 5 or 20 mg of sumatriptan in a 100-μL unit dose aqueous  
16 buffered solution containing monobasic potassium phosphate NF, anhydrous dibasic sodium  
17 phosphate USP, sulfuric acid NF, sodium hydroxide NF, and purified water USP. The pH of the  
18 solution is approximately 5.5. The osmolality of the solution is 372 or 742 mOsmol for the 5-  
19 and 20-mg IMITREX Nasal Spray, respectively.

20 **CLINICAL PHARMACOLOGY**

21 **Mechanism of Action:** Sumatriptan is an agonist for a vascular 5-hydroxytryptamine<sub>1</sub>  
22 receptor subtype (probably a member of the 5-HT<sub>1D</sub> family) having only a weak affinity for  
23 5-HT<sub>1A</sub>, 5-HT<sub>5A</sub>, and 5-HT<sub>7</sub> receptors and no significant affinity (as measured using standard  
24 radioligand binding assays) or pharmacological activity at 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, or 5-HT<sub>4</sub> receptor  
25 subtypes or at alpha<sub>1</sub>-, alpha<sub>2</sub>-, or beta-adrenergic; dopamine<sub>1</sub>; dopamine<sub>2</sub>; muscarinic; or  
26 benzodiazepine receptors.

27 The vascular 5-HT<sub>1</sub> receptor subtype that sumatriptan activates is present on cranial arteries in  
28 both dog and primate, on the human basilar artery, and in the vasculature of human dura mater  
29 and mediates vasoconstriction. This action in humans correlates with the relief of migraine  
30 headache. In addition to causing vasoconstriction, experimental data from animal studies show  
31 that sumatriptan also activates 5-HT<sub>1</sub> receptors on peripheral terminals of the trigeminal nerve  
32 innervating cranial blood vessels. Such an action may contribute to the antimigrainous effect of  
33 sumatriptan in humans.

34 In the anesthetized dog, sumatriptan selectively reduces the carotid arterial blood flow with  
35 little or no effect on arterial blood pressure or total peripheral resistance. In the cat, sumatriptan

36 selectively constricts the carotid arteriovenous anastomoses while having little effect on blood  
37 flow or resistance in cerebral or extracerebral tissues.

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

45 Protein binding, determined by equilibrium dialysis over the concentration range of 10 to  
46 1,000 ng/mL, is low, approximately 14% to 21%. The effect of sumatriptan on the protein  
47 binding of other drugs has not been evaluated, but would be expected to be minor, given the low  
48 rate of protein binding. The mean volume of distribution after subcutaneous dosing is 2.7 L/kg  
49 and the total plasma clearance is approximately 1,200 mL/min.

50 The elimination half-life of sumatriptan administered as a nasal spray is approximately  
51 2 hours, similar to the half-life seen after subcutaneous injection. Only 3% of the dose is excreted  
52 in the urine as unchanged sumatriptan; 42% of the dose is excreted as the major metabolite, the  
53 indole acetic acid analogue of sumatriptan.

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

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

59 **Hepatic Impairment:** The effect of hepatic disease on the pharmacokinetics of  
60 subcutaneously and orally administered sumatriptan has been evaluated, but the intranasal  
61 dosage form has not been studied in hepatic impairment. There were no statistically significant  
62 differences in the pharmacokinetics of subcutaneously administered sumatriptan in hepatically  
63 impaired patients compared to healthy controls. However, the liver plays an important role in the  
64 presystemic clearance of orally administered sumatriptan. In 1 small study involving oral  
65 sumatriptan in hepatically impaired patients (N = 8) matched for sex, age, and weight with  
66 healthy subjects, the hepatically impaired patients had an approximately 70% increase in AUC  
67 and  $C_{max}$  and a  $T_{max}$  40 minutes earlier compared to the healthy subjects. The bioavailability of  
68 nasally absorbed sumatriptan following intranasal administration, which would not undergo first-  
69 pass metabolism, should not be altered in hepatically impaired patients. The bioavailability of the  
70 swallowed portion of the intranasal sumatriptan dose has not been determined, but would be  
71 increased in these patients. The swallowed intranasal dose is small, however, compared to the  
72 usual oral dose, so that its impact should be minimal.

73 **Age:** The pharmacokinetics of oral sumatriptan in the elderly (mean age: 72 years, 2 males  
74 and 4 females) and in patients with migraine (mean age: 38 years, 25 males and 155 females)

75 were similar to that in healthy male subjects (mean age: 30 years). Intranasal sumatriptan has not  
76 been evaluated for age differences (see PRECAUTIONS: Geriatric Use).

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

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

83 MAOI interaction studies have not been performed with intranasal sumatriptan. Due to gut  
84 and hepatic metabolic first-pass effects, the increase of systemic exposure after coadministration  
85 of an MAO-A inhibitor with oral sumatriptan is greater than after coadministration of the MAOI  
86 with subcutaneous sumatriptan. The effects of an MAOI on systemic exposure after intranasal  
87 sumatriptan would be expected to be greater than the effect after subcutaneous sumatriptan but  
88 smaller than the effect after oral sumatriptan because only swallowed drug would be subject to  
89 first-pass effects.

90 In a study of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the  
91 clearance of subcutaneous sumatriptan. Under the conditions of this experiment, the result was a  
92 2-fold increase in the area under the sumatriptan plasma concentration x time curve (AUC),  
93 corresponding to a 40% increase in elimination half-life. This interaction was not evident with an  
94 MAO-B inhibitor.

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

98 **Xylometazoline:** An in vivo drug interaction study indicated that 3 drops of xylometazoline  
99 (0.1% w/v), a decongestant, administered 15 minutes prior to a 20-mg nasal dose of sumatriptan  
100 did not alter the pharmacokinetics of sumatriptan.

## 101 CLINICAL TRIALS

102 The efficacy of IMITREX Nasal Spray in the acute treatment of migraine headaches was  
103 demonstrated in 8, randomized, double-blind, placebo-controlled studies, of which 5 used the  
104 recommended dosing regimen and used the marketed formulation. Patients enrolled in these 5  
105 studies were predominately female (86%) and Caucasian (95%), with a mean age of 41 (range of  
106 18 to 65). Patients were instructed to treat a moderate to severe headache. Headache response,  
107 defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was  
108 assessed up to 2 hours after dosing. Associated symptoms such as nausea, photophobia, and  
109 phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours  
110 postdose. A second dose of IMITREX Nasal Spray or other medication was allowed 2 to  
111 24 hours after the initial treatment for recurrent headache. The frequency and time to use of these  
112 additional treatments were also determined. In all studies, doses of 10 and 20 mg were compared

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

115 In all 5 trials utilizing the market formulation and recommended dosage regimen, the  
 116 percentage of patients achieving headache response 2 hours after treatment was significantly  
 117 greater among patients receiving IMITREX Nasal Spray at all doses (with one exception)  
 118 compared to those who received placebo. In 4 of the 5 studies, there was a statistically significant  
 119 greater percentage of patients with headache response at 2 hours in the 20-mg group when  
 120 compared to the lower dose groups (5 and 10 mg). There were no statistically significant  
 121 differences between the 5- and 10-mg dose groups in any study. The results from the 5 controlled  
 122 clinical trials are summarized in Table 1. Note that, in general, comparisons of results obtained in  
 123 studies conducted under different conditions by different investigators with different samples of  
 124 patients are ordinarily unreliable for purposes of quantitative comparison.  
 125

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

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

128 <sup>a</sup>p<0.05 in comparison with placebo.

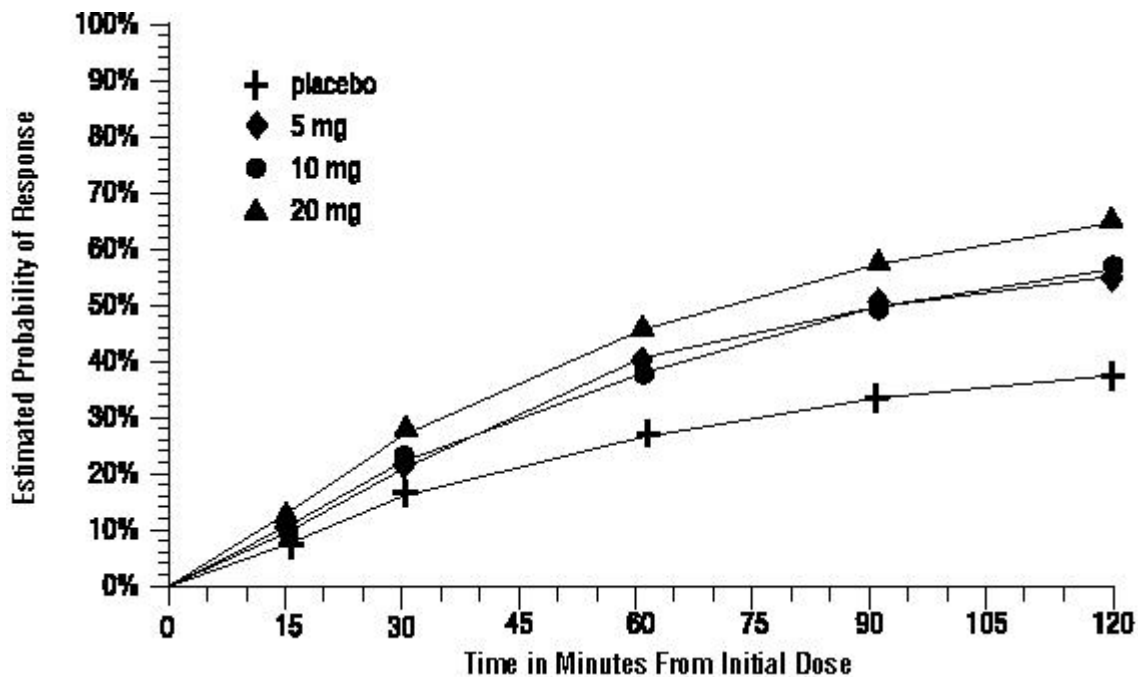
129 <sup>b</sup>p<0.05 in comparison with 10 mg.

130 <sup>c</sup>p<0.05 in comparison with 5 mg.

131 <sup>d</sup>Data are for attack 1 only of multiattack study for comparison.  
 132

133 The estimated probability of achieving an initial headache response over the 2 hours following  
 134 treatment is depicted in Figure 1.  
 135

136 **Figure 1. Estimated Probability of Achieving Initial Headache Response Within**  
137 **120 Minutes<sup>a</sup>**  
138



139  
140 <sup>a</sup> The figure shows the probability over time of obtaining headache response (no or mild  
141 pain) following treatment with intranasal sumatriptan. The averages displayed are  
142 based on pooled data from the 5 clinical controlled trials providing evidence of  
143 efficacy. Kaplan-Meier plot with patients not achieving response within 120 minutes  
144 censored to 120 minutes.

145  
146 For patients with migraine-associated nausea, photophobia, and phonophobia at baseline,  
147 there was a lower incidence of these symptoms at 2 hours following administration of IMITREX  
148 Nasal Spray compared to placebo.

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

154

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