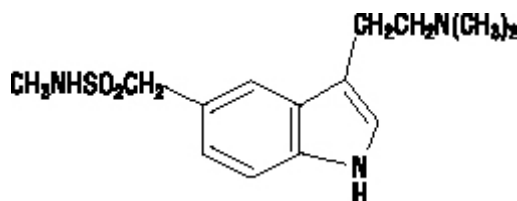


## PRESCRIBING INFORMATION

# IMITREX<sup>®</sup> (sumatriptan) Nasal Spray

### DESCRIPTION

IMITREX (sumatriptan) Nasal Spray contains sumatriptan, a selective 5-hydroxytryptamine<sub>1</sub> 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<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>S, 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- $\mu$ L 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<sub>1</sub> receptor subtype (probably a member of the 5-HT<sub>1D</sub> family) having only a weak affinity for 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 radioligand binding assays) or pharmacological activity at 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, or 5-HT<sub>4</sub> receptor subtypes or at alpha<sub>1</sub>-, alpha<sub>2</sub>-, or beta-adrenergic; dopamine<sub>1</sub>; dopamine<sub>2</sub>; muscarinic; or benzodiazepine receptors.

The vascular 5-HT<sub>1</sub> 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<sub>1</sub> 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

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.

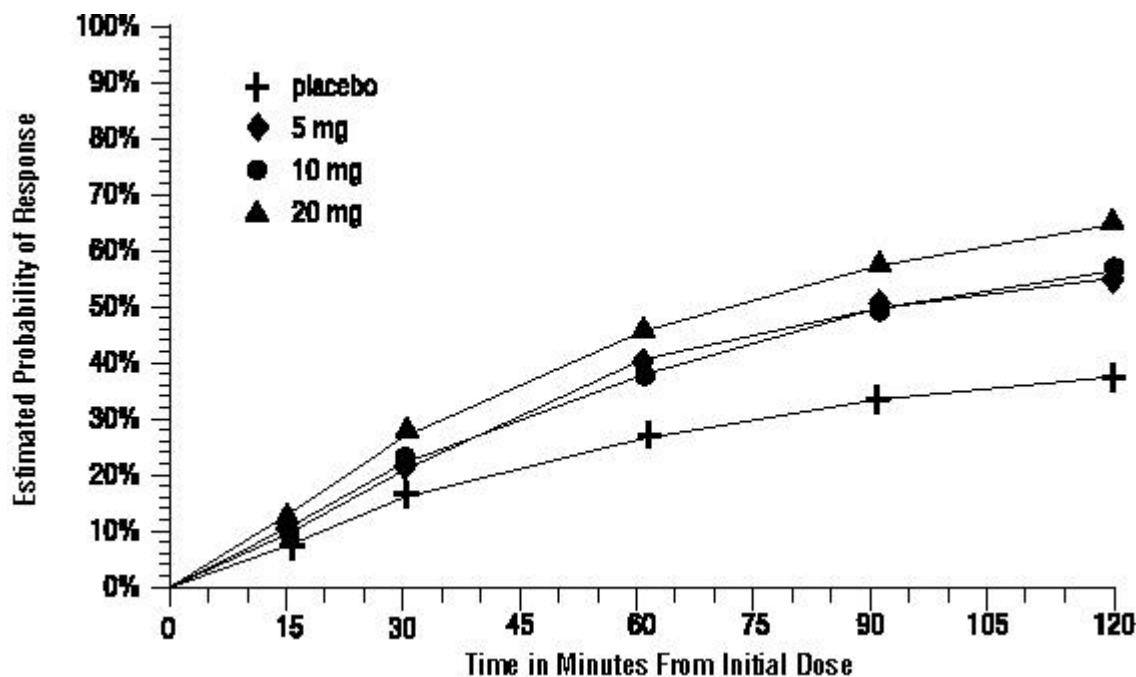
131 <sup>d</sup>Data are for attack 1 only of multiattack study for comparison.

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



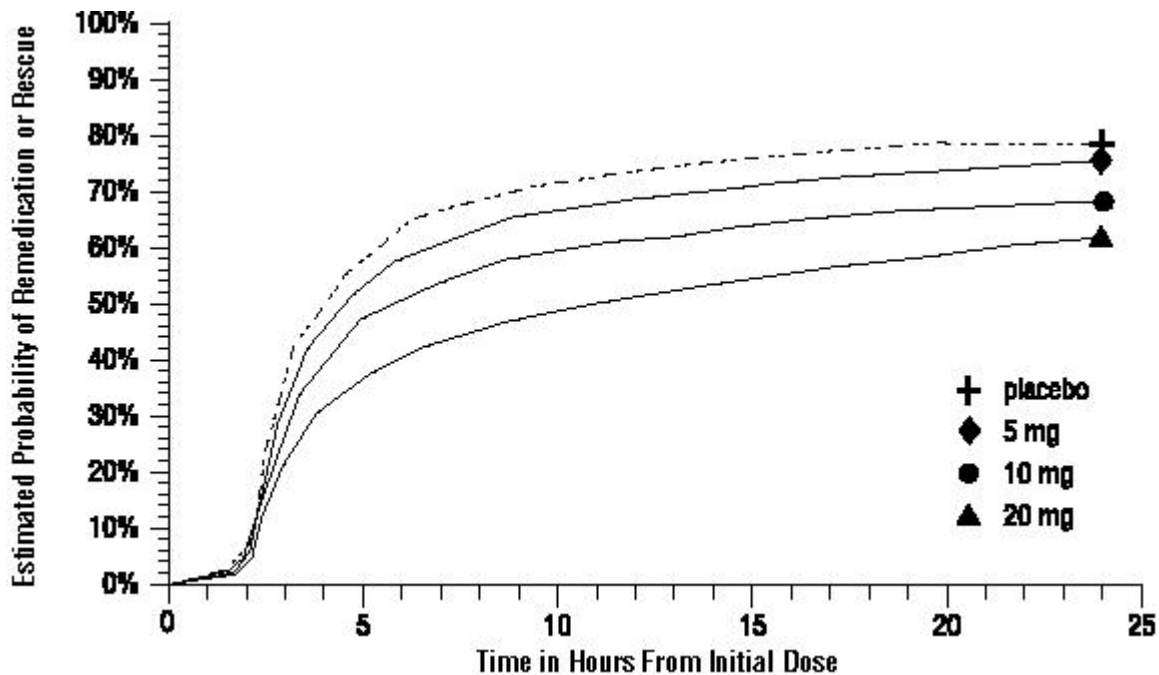
139  
140 <sup>a</sup> The figure shows the probability over time of obtaining headache response (no or mild  
141 pain) following treatment with intranasal sumatriptan. The averages displayed are  
142 based on pooled data from the 5 clinical controlled trials providing evidence of  
143 efficacy. Kaplan-Meier 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

155 **Figure 2. The Estimated Probability of Patients Taking a Second Dose or Other**  
156 **Medication for Migraine Over the 24 Hours Following the Initial Dose of Study**  
157 **Treatment<sup>a</sup>**  
158



159  
160 <sup>a</sup> Kaplan-Meier plot based on data obtained in the 3 clinical controlled trials providing  
161 evidence of efficacy with patients not using additional treatments censored to 24 hours.  
162 Plot also includes patients who had no response to the initial dose. No remediation  
163 was allowed within 2 hours postdose.  
164

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

## 172 **INDICATIONS AND USAGE**

173 IMITREX Nasal Spray is indicated for the acute treatment of migraine attacks with or without  
174 aura in adults.

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

179 **CONTRAINDICATIONS**

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

189 **Because IMITREX Nasal Spray may increase blood pressure, it should not be given to**  
190 **patients with uncontrolled hypertension.**

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

194 **IMITREX Nasal Spray and any ergotamine-containing or ergot-type medication (like**  
195 **dihydroergotamine or methysergide) should not be used within 24 hours of each other, nor**  
196 **should IMITREX Nasal Spray and another 5-HT<sub>1</sub> agonist.**

197 **IMITREX Nasal Spray should not be administered to patients with hemiplegic or**  
198 **basilar migraine.**

199 **IMITREX Nasal Spray is contraindicated in patients with hypersensitivity to**  
200 **sumatriptan or any of its components.**

201 **IMITREX Nasal Spray is contraindicated in patients with severe hepatic impairment.**

202 **WARNINGS**

203 **IMITREX Nasal Spray should only be used where a clear diagnosis of migraine**  
204 **headache has been established.**

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

217 with, coronary artery vasospasm or myocardial ischemia, sumatriptan should not be  
218 administered (see CONTRAINDICATIONS).

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

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

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

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

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

243 **Premarketing Experience With Sumatriptan:** Among approximately 4,000 patients  
244 with migraine who participated in premarketing controlled and uncontrolled clinical trials of  
245 sumatriptan nasal spray, 1 patient experienced an asymptomatic subendocardial infarction  
246 possibly subsequent to a coronary vasospastic event.

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

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

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

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

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

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

284 **Other Vasospasm-Related Events:** Sumatriptan may cause vasospastic reactions other than  
285 coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with  
286 abdominal pain and bloody diarrhea have been reported. Very rare reports of transient and  
287 permanent blindness and significant partial vision loss have been reported with the use of  
288 sumatriptan. Visual disorders may also be part of a migraine attack.

289 **Serotonin Syndrome:** Serotonin syndrome may occur with triptans, including IMITREX,  
290 particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or  
291 serotonin norepinephrine reuptake inhibitors (SNRIs). Serotonin syndrome symptoms may  
292 include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g.,  
293 tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia,  
294 incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of  
295 symptoms can occur within minutes to hours of receiving a new or a greater dose of a

296 serotonergic medication. Treatment with IMITREX should be discontinued if serotonin  
297 syndrome is suspected.

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

304 **Local Irritation:** Of the 3,378 patients using the nasal spray (5-, 10-, or 20-mg doses) on 1 or 2  
305 occasions in controlled clinical studies, approximately 5% noted irritation in the nose and throat.  
306 Irritative symptoms such as burning, numbness, paresthesia, discharge, and pain or soreness were  
307 noted to be severe in about 1% of patients treated. The symptoms were transient and in  
308 approximately 60% of the cases, the symptoms resolved in less than 2 hours. Limited  
309 examinations of the nose and throat did not reveal any clinically noticeable injury in these  
310 patients.

311 The consequences of extended and repeated use of IMITREX Nasal Spray on the nasal and/or  
312 respiratory mucosa have not been systematically evaluated in patients. No increase in the  
313 incidence of local irritation was observed in patients using IMITREX Nasal Spray repeatedly for  
314 up to 1 year.

315 In inhalation studies in rats dosed daily for up to 1 month at exposures as low as one half the  
316 maximum daily human exposure (based on dose per surface area of nasal cavity), epithelial  
317 hyperplasia (with and without keratinization) and squamous metaplasia were observed in the  
318 larynx at all doses tested. These changes were partially reversible after a 2-week drug-free  
319 period. When dogs were dosed daily with various formulations by intranasal instillation for up to  
320 13 weeks at exposures of 2 to 4 times the maximum daily human exposure (based on dose per  
321 surface area of nasal cavity), respiratory and nasal mucosa exhibited evidence of epithelial  
322 hyperplasia, focal squamous metaplasia, granulomata, bronchitis, and fibrosing alveolitis. A no-  
323 effect dose was not established. The changes observed in both species are not considered to be  
324 signs of either preneoplastic or neoplastic transformation.

325 Local effects on nasal and respiratory tissues after chronic intranasal dosing in animals have  
326 not been studied.

327 **Concomitant Drug Use:** In patients taking MAO-A inhibitors, sumatriptan plasma levels  
328 attained after treatment with recommended doses are 2-fold (following subcutaneous  
329 administration) to 7-fold (following oral administration) higher than those obtained under other  
330 conditions. Accordingly, the coadministration of IMITREX Nasal Spray and an MAO-A  
331 inhibitor is contraindicated (see CLINICAL PHARMACOLOGY and  
332 CONTRAINDICATIONS).

333 **Hypersensitivity:** Hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred on  
334 rare occasions in patients receiving sumatriptan. Such reactions can be life threatening or fatal. In

335 general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history  
336 of sensitivity to multiple allergens (see CONTRAINDICATIONS).

### 337 **PRECAUTIONS**

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

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

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

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

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

363 **Overuse:** Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or a combination  
364 of drugs for 10 or more days per month) may lead to exacerbation of headache (medication  
365 overuse headache). Medication overuse headache may present as migraine-like daily headaches,  
366 or as a marked increase in frequency of migraine attacks. Detoxification of patients, including  
367 withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes  
368 a transient worsening of headache) may be necessary. Migraine patients should be informed  
369 about the risks of medication overuse and encouraged to record headache frequency and drug  
370 use.

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

373 Patients should be cautioned about the risk of serotonin syndrome with the use of sumatriptan  
374 or other triptans, especially during combined use with SSRIs or SNRIs.

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

377 **Drug Interactions: *Selective Serotonin Reuptake Inhibitors/Serotonin***  
378 ***Norepinephrine Reuptake Inhibitors and Serotonin Syndrome:*** Cases of life-  
379 threatening serotonin syndrome have been reported during combined use of SSRIs or SNRIs and  
380 triptans (see WARNINGS).

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

386 ***Monoamine Oxidase-A Inhibitors:*** MAO-A inhibitors reduce sumatriptan clearance,  
387 significantly increasing systemic exposure. Therefore, the use of IMITREX Nasal Spray in  
388 patients receiving MAO-A inhibitors is contraindicated (see CLINICAL PHARMACOLOGY  
389 and CONTRAINDICATIONS).

390 **Drug/Laboratory Test Interactions:** IMITREX Nasal Spray is not known to interfere with  
391 commonly employed clinical laboratory tests.

392 **Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:*** In  
393 carcinogenicity studies, rats and mice were given sumatriptan by oral gavage (rats: 104 weeks)  
394 or drinking water (mice: 78 weeks). Average exposures achieved in mice receiving the highest  
395 dose (target dose of 160 mg/kg/day) were approximately 184 times the exposure attained in  
396 humans after the maximum recommended single intranasal dose of 20 mg. The highest dose  
397 administered to rats (160 mg/kg/day, reduced from 360 mg/kg/day during week 21) was  
398 approximately 78 times the maximum recommended single intranasal dose of 20 mg on a mg/m<sup>2</sup>  
399 basis. There was no evidence of an increase in tumors in either species related to sumatriptan  
400 administration. Local effects on nasal and respiratory tissue after chronic intranasal dosing in  
401 animals have not been evaluated (see WARNINGS).

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

407 ***Impairment of Fertility:*** In a study in which male and female rats were dosed daily with  
408 oral sumatriptan prior to and throughout the mating period, there was a treatment-related  
409 decrease in fertility secondary to a decrease in mating in animals treated with 50 and  
410 500 mg/kg/day. The highest no-effect dose for this finding was 5 mg/kg/day, or approximately  
411 twice the maximum recommended single human intranasal dose of 20 mg on a mg/m<sup>2</sup> basis. It is  
412 not clear whether the problem is associated with treatment of the males or females or both

413 combined. In a similar study by the subcutaneous route there was no evidence of impaired  
414 fertility at 60 mg/kg/day, the maximum dose tested, which is equivalent to approximately  
415 29 times the maximum recommended single human intranasal dose of 20 mg on a  $\text{mg}/\text{m}^2$  basis.  
416 Fertility studies, in which sumatriptan was administered by the intranasal route, were not  
417 conducted.

418 **Pregnancy:** Pregnancy Category C. In reproductive toxicity studies in rats and rabbits, oral  
419 treatment with sumatriptan was associated with embryoletality, fetal abnormalities, and pup  
420 mortality. When administered by the intravenous route to rabbits, sumatriptan has been shown to  
421 be embryoletal. Reproductive toxicity studies for sumatriptan by the intranasal route have not  
422 been conducted.

423 There are no adequate and well-controlled studies in pregnant women. Therefore, IMITREX  
424 Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential  
425 risk to the fetus. In assessing this information, the following findings should be considered.

426 **Embryoletality:** When given orally or intravenously to pregnant rabbits daily throughout  
427 the period of organogenesis, sumatriptan caused embryoletality at doses at or close to those  
428 producing maternal toxicity. In the oral studies this dose was 100 mg/kg/day, and in the  
429 intravenous studies this dose was 2.0 mg/kg/day. The mechanism of the embryoletality is not  
430 known. The highest no-effect dose for embryoletality by the oral route was 50 mg/kg/day,  
431 which is approximately 48 times the maximum single recommended human intranasal dose of  
432 20 mg on a  $\text{mg}/\text{m}^2$  basis. By the intravenous route, the highest no-effect dose was  
433 0.75 mg/kg/day, or approximately 0.7 times the maximum single recommended human intranasal  
434 dose of 20 mg on a  $\text{mg}/\text{m}^2$  basis.

435 The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at  
436 12.5 mg/kg/day, the maximum dose tested, did not cause embryoletality. This dose is  
437 approximately 6 times the maximum single recommended human intranasal dose of 20 mg on a  
438  $\text{mg}/\text{m}^2$  basis. Additionally, in a study in rats given subcutaneous sumatriptan daily, prior to and  
439 throughout pregnancy, at 60 mg/kg/day, the maximum dose tested, there was no evidence of  
440 increased embryo/fetal lethality. This dose is equivalent to approximately 29 times the  
441 maximum recommended single human intranasal dose of 20 mg on a  $\text{mg}/\text{m}^2$  basis.

442 **Teratogenicity:** Oral treatment of pregnant rats with sumatriptan during the period of  
443 organogenesis resulted in an increased incidence of blood vessel abnormalities (cervicothoracic  
444 and umbilical) at doses of approximately 250 mg/kg/day or higher. The highest no-effect dose  
445 was approximately 60 mg/kg/day, which is approximately 29 times the maximum single  
446 recommended human intranasal dose of 20 mg on a  $\text{mg}/\text{m}^2$  basis. Oral treatment of pregnant  
447 rabbits with sumatriptan during the period of organogenesis resulted in an increased incidence of  
448 cervicothoracic vascular and skeletal abnormalities. The highest no-effect dose for these effects  
449 was 15 mg/kg/day, or approximately 14 times the maximum single recommended human  
450 intranasal dose of 20 mg on a  $\text{mg}/\text{m}^2$  basis.

451 A study in which rats were dosed daily with oral sumatriptan prior to and throughout gestation  
452 demonstrated embryo/fetal toxicity (decreased body weight, decreased ossification, increased

453 incidence of rib variations) and an increased incidence of a syndrome of malformations (short  
454 tail/short body and vertebral disorganization) at 500 mg/kg/day. The highest no-effect dose was  
455 50 mg/kg/day, or approximately 24 times the maximum single recommended human intranasal  
456 dose of 20 mg on a mg/m<sup>2</sup> basis. In a study in rats dosed daily with subcutaneous sumatriptan  
457 prior to and throughout pregnancy, at a dose of 60 mg/kg/day, the maximum dose tested, there  
458 was no evidence of teratogenicity. This dose is equivalent to approximately 29 times the  
459 maximum recommended single human intranasal dose of 20 mg on a mg/m<sup>2</sup> basis.

460 **Pup Deaths:** Oral treatment of pregnant rats with sumatriptan during the period of  
461 organogenesis resulted in a decrease in pup survival between birth and postnatal day 4 at doses  
462 of approximately 250 mg/kg/day or higher. The highest no-effect dose for this effect was  
463 approximately 60 mg/kg/day, or 29 times the maximum single recommended human intranasal  
464 dose of 20 mg on a mg/m<sup>2</sup> basis.

465 Oral treatment of pregnant rats with sumatriptan from gestational day 17 through postnatal  
466 day 21 demonstrated a decrease in pup survival measured at postnatal days 2, 4, and 20 at the  
467 dose of 1,000 mg/kg/day. The highest no-effect dose for this finding was 100 mg/kg/day,  
468 approximately 49 times the maximum single recommended human intranasal dose of 20 mg on a  
469 mg/m<sup>2</sup> basis. In a similar study in rats by the subcutaneous route there was no increase in pup  
470 death at 81 mg/kg/day, the highest dose tested, which is equivalent to 40 times the maximum  
471 single recommended human intranasal dose of 20 mg on a mg/m<sup>2</sup> basis.

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

475 **Nursing Mothers:** Sumatriptan is excreted in human breast milk following subcutaneous  
476 administration. Infant exposure to sumatriptan can be minimized by avoiding breastfeeding for  
477 12 hours after treatment with IMITREX Nasal Spray.

478 **Pediatric Use:** Safety and effectiveness of IMITREX Nasal Spray in pediatric patients under  
479 18 years of age have not been established; therefore, IMITREX Nasal Spray is not recommended  
480 for use in patients under 18 years of age.

481 Two controlled clinical trials evaluating sumatriptan nasal spray (5 to 20 mg) in pediatric  
482 patients aged 12 to 17 years enrolled a total of 1,248 adolescent migraineurs who treated a single  
483 attack. The studies did not establish the efficacy of sumatriptan nasal spray compared to placebo  
484 in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were  
485 similar in nature to those reported in clinical trials in adults.

486 Five controlled clinical trials (2 single attack studies, 3 multiple attack studies) evaluating oral  
487 sumatriptan (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701  
488 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared  
489 to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical  
490 trials were similar in nature to those reported in clinical trials in adults. The frequency of all  
491 adverse events in these patients appeared to be both dose- and age-dependent, with younger  
492 patients reporting events more commonly than older adolescents.

493 Postmarketing experience documents that serious adverse events have occurred in the  
494 pediatric population after use of subcutaneous, oral, and/or intranasal sumatriptan. These reports  
495 include events similar in nature to those reported rarely in adults, including stroke, visual loss,  
496 and death. A myocardial infarction has been reported in a 14-year-old male following the use of  
497 oral sumatriptan; clinical signs occurred within 1 day of drug administration. Since clinical data  
498 to determine the frequency of serious adverse events in pediatric patients who might receive  
499 injectable, oral, or intranasal sumatriptan are not presently available, the use of sumatriptan in  
500 patients aged younger than 18 years is not recommended.

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

## 504 **ADVERSE REACTIONS**

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

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

513 **Incidence in Controlled Clinical Trials:** Among 3,653 patients treated with IMITREX  
514 Nasal Spray in active- and placebo-controlled clinical trials, less than 0.4% of patients withdrew  
515 for reasons related to adverse events. Table 2 lists adverse events that occurred in worldwide  
516 placebo-controlled clinical trials in 3,419 migraineurs. The events cited reflect experience gained  
517 under closely monitored conditions of clinical trials in a highly selected patient population. In  
518 actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the  
519 conditions of use, reporting behavior, and the kinds of patients treated may differ.

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

523

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

Adverse Event Type	Percent of Patients Reporting			
	Placebo (n = 704)	IMITREX 5 mg (n = 496)	IMITREX 10 mg (n = 1,007)	IMITREX 20 mg (n = 1,212)
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%

526

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

528

529 IMITREX Nasal Spray is generally well tolerated. Across all doses, most adverse reactions  
530 were mild and transient and did not lead to long-lasting effects. The incidence of adverse events  
531 in controlled clinical trials was not affected by gender, weight, or age of the patients; use of  
532 prophylactic medications; or presence of aura. There were insufficient data to assess the impact  
533 of race on the incidence of adverse events.

533

**Other Events Observed in Association With the Administration of IMITREX Nasal  
534 Spray:** In the paragraphs that follow, the frequencies of less commonly reported adverse clinical  
535 events are presented. Because the reports include events observed in open and uncontrolled  
536 studies, the role of IMITREX Nasal Spray in their causation cannot be reliably determined.  
537 Furthermore, variability associated with adverse event reporting, the terminology used to  
538 describe adverse events, etc., limit the value of the quantitative frequency estimates provided.  
539 Event frequencies are calculated as the number of patients who used IMITREX Nasal Spray (5,  
540 10, or 20 mg in controlled and uncontrolled trials) and reported an event divided by the total  
541 number of patients (N = 3,711) exposed to IMITREX Nasal Spray. All reported events are  
542 included except those already listed in the previous table, those too general to be informative,  
543 and those not reasonably associated with the use of the drug. Events are further classified within  
544 body system categories and enumerated in order of decreasing frequency using the following  
545 definitions: infrequent adverse events are those occurring in 1/100 to 1/1,000 patients and rare  
546 adverse events are those occurring in fewer than 1/1,000 patients.

547 **Atypical Sensations:** Infrequent were tingling, warm/hot sensation, numbness, pressure  
548 sensation, feeling strange, feeling of heaviness, feeling of tightness, paresthesia, cold sensation,  
549 and tight feeling in head. Rare were dysesthesia and prickling sensation.

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

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

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

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

560 **Eye:** Infrequent were irritation of eyes and visual disturbance.

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

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

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

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

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

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

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

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

582 **Other Events Observed in the Clinical Development of IMITREX:** The following  
583 adverse events occurred in clinical trials with IMITREX Injection and IMITREX Tablets.  
584 Because the reports include events observed in open and uncontrolled studies, the role of  
585 IMITREX in their causation cannot be reliably determined. All reported events are included

586 except those already listed, those too general to be informative, and those not reasonably  
587 associated with the use of the drug.

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

590 **Cardiovascular:** Abnormal pulse, angina, atherosclerosis, cerebral ischemia,  
591 cerebrovascular lesion, heart block, peripheral cyanosis, pulsating sensations, Raynaud  
592 syndrome, thrombosis, transient myocardial ischemia, various transient ECG changes  
593 (nonspecific ST or T wave changes, prolongation of PR or QTc intervals, sinus arrhythmia,  
594 nonsustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats,  
595 delayed activation of the right ventricle), and vasodilation.

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

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

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

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

609 **Hematological Disorders:** Anemia.

#### 610 **Injection Site Reaction**

611 **Miscellaneous:** Contusions, fluid retention, hematoma, hypersensitivity to various agents,  
612 jaw discomfort, miscellaneous laboratory abnormalities, overdose, “serotonin agonist effect,”  
613 and speech disturbance.

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

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

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

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

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

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

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

643 **Blood:** Hemolytic anemia, pancytopenia, thrombocytopenia.

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

646 **Ear, Nose, and Throat:** Deafness.

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

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

650 **Hepatic:** Elevated liver function tests.

651 **Neurological:** Central nervous system vasculitis, cerebrovascular accident, dysphasia,  
652 serotonin syndrome, subarachnoid hemorrhage.

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

655 **Psychiatry:** Panic disorder.

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

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

660 **Urogenital:** Acute renal failure.

## 661 **DRUG ABUSE AND DEPENDENCE**

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

665 **OVERDOSAGE**

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

670 Overdose in animals has been fatal and has been heralded by convulsions, tremor, paralysis,  
671 inactivity, ptosis, erythema of the extremities, abnormal respiration, cyanosis, ataxia, mydriasis,  
672 salivation, and lacrimation. The elimination half-life of sumatriptan is about 2 hours (see  
673 CLINICAL PHARMACOLOGY), and therefore monitoring of patients after overdose with  
674 IMITREX Nasal Spray should continue for at least 10 hours or while symptoms or signs persist.  
675 It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of  
676 sumatriptan.

677 **DOSAGE AND ADMINISTRATION**

678 In controlled clinical trials, single doses of 5, 10, or 20 mg of IMITREX Nasal Spray  
679 administered into 1 nostril were effective for the acute treatment of migraine in adults. A greater  
680 proportion of patients had headache response following a 20-mg dose than following a 5- or  
681 10-mg dose (see CLINICAL TRIALS). Individuals may vary in response to doses of IMITREX  
682 Nasal Spray. The choice of dose should therefore be made on an individual basis, weighing the  
683 possible benefit of the 20-mg dose with the potential for a greater risk of adverse events. A  
684 10-mg dose may be achieved by the administration of a single 5-mg dose in each nostril. There is  
685 evidence that doses above 20 mg do not provide a greater effect than 20 mg.

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

689 **HOW SUPPLIED**

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

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

694 **ANIMAL TOXICOLOGY**

695 **Corneal Opacities:** Dogs receiving oral sumatriptan developed corneal opacities and defects  
696 in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day,  
697 and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a  
698 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses  
699 were not established; however, the relative exposure at the lowest dose tested was approximately  
700 5 times the human exposure after a 100-mg oral dose or 3 times the human exposure after a 6-mg  
701 subcutaneous dose or 22 times the human exposure after a single 20-mg intranasal dose. There is  
702 evidence of alterations in corneal appearance on the first day of intranasal dosing to dogs.

703 Changes were noted at the lowest dose tested, which was approximately 2 times the maximum  
704 single human intranasal dose of 20 mg on a mg/m<sup>2</sup> basis.

705  
706



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709 Research Triangle Park, NC 27709

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## 715 **PATIENT INFORMATION**

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

717

718 **Patient Information**  
719 **IMITREX<sup>®</sup> (IM-i-trex)**  
720 **(sumatriptan)**  
721 **Nasal Spray**

722

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

726

727 **What is the most important information I should know about IMITREX Nasal Spray?**

728 **IMITREX Nasal Spray can cause serious side effects, including:**

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

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

- 732 • discomfort in the center of your chest that lasts for more than a few minutes, or that goes  
733 away and comes back
- 734 • chest pain or chest discomfort that feels like heavy pressure, squeezing, or fullness
- 735 • pain or discomfort in your arms, back, neck, jaw, or stomach
- 736 • shortness of breath with or without chest discomfort
- 737 • breaking out in a cold sweat
- 738 • nausea or vomiting
- 739 • feeling lightheaded

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

- 742 • have high blood pressure
- 743 • have high cholesterol levels
- 744 • smoke
- 745 • are overweight
- 746 • have diabetes
- 747 • have a family history of heart disease
- 748 • are a female who has gone through menopause
- 749 • are a male over age 40

750 **Serotonin syndrome.** Serotonin syndrome is a serious and life-threatening problem that can  
751 happen in people using IMITREX Nasal Spray, especially if IMITREX Nasal Spray is used with  
752 anti-depressant medicines called selective serotonin reuptake inhibitors (SSRIs) or selective  
753 norepinephrine reuptake inhibitors (SNRIs).

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

755 Call your healthcare provider right away if you have any of the following symptoms of serotonin  
756 syndrome:

- 757 • mental changes such as seeing things that are not there (hallucinations), agitation, or coma
- 758 • fast heartbeat
- 759 • changes in blood pressure
- 760 • high body temperature
- 761 • tight muscles
- 762 • trouble walking
- 763 • nausea, vomiting, or diarrhea

764

### 765 **What is IMITREX Nasal Spray?**

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

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

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

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

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

775

### 776 **Who should not use IMITREX Nasal Spray?**

777 **Do not use IMITREX Nasal Spray if you have:**

- 778 • heart problems or a history of heart problems
- 779 • narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular
- 780 disease)
- 781 • uncontrolled high blood pressure
- 782 • severe liver problems
- 783 • hemiplegic migraines or basilar migraines. If you are not sure if you have these types of
- 784 migraines, ask your healthcare provider.
- 785 • had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation
- 786 • taken any of the following medicines in the last 24 hours:
- 787 • almotriptan (AXERT<sup>®</sup>)
- 788 • eletriptan (RELPAX<sup>®</sup>)
- 789 • frovatriptan (FROVA<sup>®</sup>)
- 790 • naratriptan (AMERGE<sup>®</sup>)
- 791 • rizatriptan (MAXALT<sup>®</sup>, MAXALT-MLT<sup>®</sup>)
- 792 • sumatriptan and naproxen (TREXIMET<sup>®</sup>)
- 793 • ergotamines (CAFERGOT<sup>®</sup>, ERGOMAR<sup>®</sup>, MIGERGOT<sup>®</sup>)
- 794 • dihydroergotamine (D.H.E. 45<sup>®</sup>, MIGRANAL<sup>®</sup>)
- 795 Ask your doctor if you are not sure if your medicine is listed above.
- 796 • an allergy to sumatriptan or any of the ingredients in IMITREX Nasal Spray. See the end of
- 797 this leaflet for a complete list of ingredients in IMITREX Nasal Spray.
- 798

799 **What should I tell my healthcare provider before taking IMITREX Nasal Spray?**

800 Before you use IMITREX Nasal Spray, tell your healthcare provider about all of your medical

801 conditions, including if you:

- 802 • have high blood pressure
- 803 • have high cholesterol
- 804 • have diabetes
- 805 • smoke
- 806 • are overweight
- 807 • are a female who has gone through menopause
- 808 • have heart disease or a family history of heart disease or stroke
- 809 • have kidney problems
- 810 • have liver problems
- 811 • have had epilepsy or seizures
- 812 • are not using effective birth control
- 813 • are pregnant or plan to become pregnant. It is not known if IMITREX Nasal Spray will harm
- 814 your unborn baby.

- 815 • become pregnant while taking IMITREX Nasal Spray. Talk with your healthcare provider  
816 about registering with the Sumatriptan Pregnancy Registry. Your healthcare provider can  
817 enroll you in this registry by calling 1-800-336-2176.
- 818 • are breastfeeding or plan to breastfeed. IMITREX Nasal Spray passes into your breast milk  
819 and may harm your baby. Talk with your healthcare provider about the best way to feed your  
820 baby if you use IMITREX Nasal Spray.

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

823 IMITREX Nasal Spray and other medicines may affect each other, causing side effects.

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

- 825 • selective serotonin reuptake inhibitors (SSRIs)  
826 • serotonin norepinephrine reuptake inhibitors (SNRIs)  
827 • monoamine oxidase inhibitors (MAOIs)

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

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

831

832 **How should I use IMITREX Nasal Spray?**

833 Before using IMITREX Nasal Spray, read the Instructions for Use at the end of this Patient  
834 Information leaflet.

- 835 • Certain people should take their first dose of IMITREX Nasal Spray in their healthcare  
836 provider's office or in another medical setting. Ask your healthcare provider if you should  
837 take your first dose in a medical setting.
- 838 • Use IMITREX Nasal Spray exactly as your healthcare provider tells you to use it.
- 839 • Your healthcare provider may change your dose. Do not change your dose without first  
840 talking with your healthcare provider.
- 841 • If you do not get any relief after your first nasal spray, do not use a second nasal spray  
842 without first talking with your healthcare provider.
- 843 • If your headache comes back after the first nasal spray or you only get some relief from your  
844 headache, you can use a second nasal spray 2 hours after the first nasal spray.
- 845 • Do not take more than a total of 40 mg of IMITREX Nasal Spray in a 24-hour period.
- 846 • It is not known how using IMITREX Nasal Spray for a long time affects the nose and throat.
- 847 • Some people who use too much IMITREX Nasal Spray may have worse headaches  
848 (medication overuse headache). If your headaches get worse, your healthcare provider may  
849 decide to stop your treatment with IMITREX Nasal Spray.
- 850 • If you use too much IMITREX Nasal Spray, call your healthcare provider or go to the nearest  
851 hospital emergency room right away.

- 852 • You should write down when you have headaches and when you take IMITREX Nasal Spray  
853 so you can talk with your healthcare provider about how IMITREX Nasal Spray is working  
854 for you.

855

856 **What should I avoid while taking IMITREX Nasal Spray?**

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

859

860 **What are the possible side effects of IMITREX Nasal Spray?**

861 **IMITREX Nasal Spray may cause serious side effects.** See “What is the most important  
862 information I should know about IMITREX Nasal Spray?”

863 These serious side effects include:

- 864 • changes in color or sensation in your fingers and toes (Raynaud’s syndrome)  
865 • stomach and intestinal problems (gastrointestinal and colonic ischemic events). Symptoms of  
866 gastrointestinal and colonic ischemic events include:  
867 • sudden or severe stomach pain  
868 • stomach pain after meals  
869 • weight loss  
870 • nausea or vomiting  
871 • constipation or diarrhea  
872 • bloody diarrhea  
873 • fever  
874 • problems with blood circulation to your legs and feet (peripheral vascular ischemia).  
875 Symptoms of peripheral vascular ischemia include:  
876 • cramping and pain in your legs or hips  
877 • feeling of heaviness or tightness in your leg muscles  
878 • burning or aching pain in your feet or toes while resting  
879 • numbness, tingling, or weakness in your legs  
880 • cold feeling or color changes in 1 or both legs or feet  
881 • shortness of breath or wheezing  
882 • hives (itchy bumps); swelling of your tongue, mouth, or throat

883 The most common side effects of IMITREX Nasal Spray include:

- 884 • dizziness  
885 • warm, hot, burning feeling to your face (flushing)  
886 • discomfort of your neck, throat, or nose  
887 • unusual or bad taste in your mouth  
888 • feeling weak, drowsy, or tired  
889 • sensitivity to loud noises

890 Tell your healthcare provider if you have any side effect that bothers you or that does not go  
891 away.

892 These are not all the possible side effects of IMITREX Nasal Spray. For more information, ask  
893 your healthcare provider or pharmacist.

894 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-  
895 800-FDA-1088.

896

897 **How should I store IMITREX Nasal Spray?**

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

900 **Keep IMITREX Nasal Spray and all medicines out of the reach of children.**

901

902 **General information about the safe and effective use of IMITREX Nasal Spray.**

903 Medicines are sometimes prescribed for purposes other than those listed in Patient Information  
904 leaflets. Do not use IMITREX Nasal Spray for a condition for which it was not prescribed. Do  
905 not give IMITREX Nasal Spray to other people, even if they have the same symptoms you have.  
906 It may harm them.

907 This Patient Information leaflet summarizes the most important information about IMITREX  
908 Nasal Spray. If you would like more information, talk with your healthcare provider. You can  
909 ask your healthcare provider or pharmacist for information about IMITREX Nasal Spray that is  
910 written for healthcare professionals.

911 For more information, go to [www.gsk.com](http://www.gsk.com) or call 1-888-825-5249.

912

913 **What are the ingredients in IMITREX Nasal Spray?**

914 Active ingredient: sumatriptan

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

917


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922

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

924

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