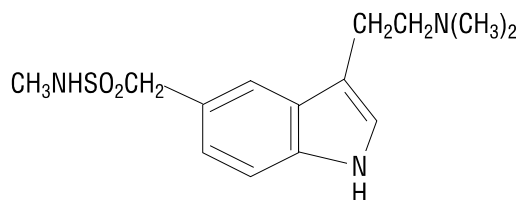


PRESCRIBING INFORMATION

1 2 **IMITREX[®]** 3 **(sumatriptan)** 4 **Nasal Spray** 5

6 **DESCRIPTION**

7 IMITREX (sumatriptan) Nasal Spray contains sumatriptan, a selective 5-hydroxytryptamine₁
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:
10



11
12
13 The empirical formula is C₁₄H₂₁N₃O₂S, 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-hydroxytryptamine₁
22 receptor subtype (probably a member of the 5-HT_{1D} family) having only a weak affinity for
23 5-HT_{1A}, 5-HT_{5A}, and 5-HT₇ receptors and no significant affinity (as measured using standard
24 radioligand binding assays) or pharmacological activity at 5-HT₂, 5-HT₃, or 5-HT₄ receptor
25 subtypes or at alpha₁-, alpha₂-, or beta-adrenergic; dopamine₁; dopamine₂; muscarinic; or
26 benzodiazepine receptors.

27 The vascular 5-HT₁ 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-HT₁ 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
69 first-pass metabolism, should not be altered in hepatically impaired patients. The bioavailability
70 of the swallowed portion of the intranasal sumatriptan dose has not been determined, but would
71 be 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.

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%* (N = 121)	46%* (N = 112)	64%*†‡ (N = 118)
Study 2	25% (N = 138)	Not applicable	44%* (N = 273)	55%*† (N = 277)
Study 3	35% (N = 100)	Not applicable	54%* (N = 106)	63%* (N = 202)
Study 4	29% (N = 112)	Not applicable	43% (N = 106)	62%*† (N = 215)
Study 5 [§]	36% (N = 198)	45%* (N = 296)	53%* (N = 291)	60%*‡ (N = 286)

* p<0.05 in comparison with placebo.

† p<0.05 in comparison with 10 mg.

‡ p<0.05 in comparison with 5 mg.

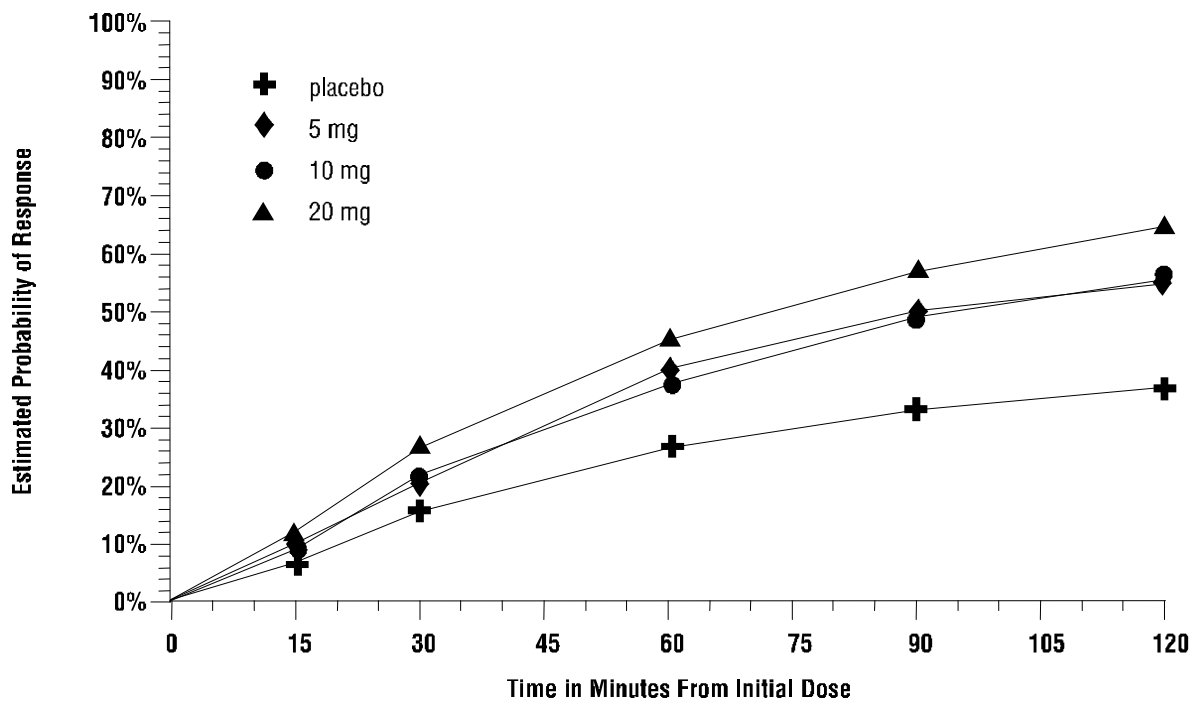
§ Data are for attack 1 only of multiattack study for comparison.

128
 129 The estimated probability of achieving an initial headache response over the 2 hours following
 130 treatment is depicted in Figure 1.

131

132 **Figure 1. Estimated Probability of Achieving Initial Headache Response Within**
133 **120 Minutes** *

134



135

136

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

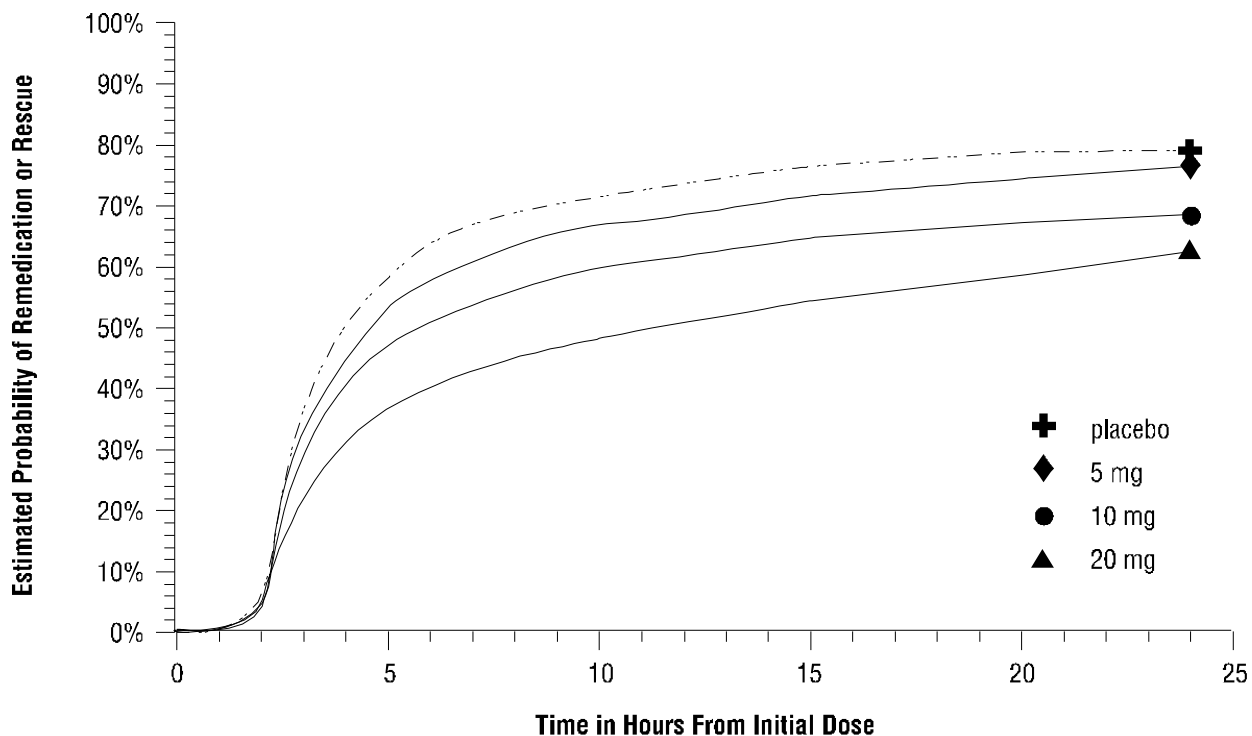
142

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

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

151

152 **Figure 2. The Estimated Probability of Patients Taking a Second Dose or Other Medication**
 153 **for Migraine Over the 24 Hours Following the Initial Dose of Study Treatment ***
 154



155
 156
 157 * Kaplan-Meier plot based on data obtained in the 3 clinical controlled trials providing evidence
 158 of efficacy with patients not using additional treatments censored to 24 hours. Plot also
 159 includes patients who had no response to the initial dose. No remedication was allowed within
 160 2 hours postdose.

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

168 **INDICATIONS AND USAGE**

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

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

175 **CONTRAINDICATIONS**

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

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

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

190 **IMITREX Nasal Spray and any ergotamine-containing or ergot-type medication (like**
191 **dihydroergotamine or methysergide) should not be used within 24 hours of each other, nor**
192 **should IMITREX Nasal Spray and another 5-HT₁ agonist.**

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

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

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

198 **WARNINGS**

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

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

213 of, or consistent with, coronary artery vasospasm or myocardial ischemia, sumatriptan
214 should not be administered (see CONTRAINDICATIONS).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

289 **Local Irritation:** Of the 3,378 patients using the nasal spray (5-, 10-, or 20-mg doses) on 1 or 2
290 occasions in controlled clinical studies, approximately 5% noted irritation in the nose and throat.
291 Irritative symptoms such as burning, numbness, paresthesia, discharge, and pain or soreness were
292 noted to be severe in about 1% of patients treated. The symptoms were transient and in

293 approximately 60% of the cases, the symptoms resolved in less than 2 hours. Limited
294 examinations of the nose and throat did not reveal any clinically noticeable injury in these
295 patients.

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

300 In inhalation studies in rats dosed daily for up to 1 month at exposures as low as one half the
301 maximum daily human exposure (based on dose per surface area of nasal cavity), epithelial
302 hyperplasia (with and without keratinization) and squamous metaplasia were observed in the
303 larynx at all doses tested. These changes were partially reversible after a 2-week drug-free
304 period. When dogs were dosed daily with various formulations by intranasal instillation for up to
305 13 weeks at exposures of 2 to 4 times the maximum daily human exposure (based on dose per
306 surface area of nasal cavity), respiratory and nasal mucosa exhibited evidence of epithelial
307 hyperplasia, focal squamous metaplasia, granulomata, bronchitis, and fibrosing alveolitis. A
308 no-effect dose was not established. The changes observed in both species are not considered to
309 be signs of either preneoplastic or neoplastic transformation.

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

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

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

322 **PRECAUTIONS**

323 **General:** Chest discomfort and jaw or neck tightness have been reported infrequently following
324 the administration of IMITREX Nasal Spray and have also been reported following use of
325 IMITREX Tablets. Chest, jaw, or neck tightness is relatively common after administration of
326 IMITREX Injection. Only rarely have these symptoms been associated with ischemic ECG
327 changes. However, because sumatriptan may cause coronary artery vasospasm, patients who
328 experience signs or symptoms suggestive of angina following sumatriptan should be evaluated
329 for the presence of CAD or a predisposition to Prinzmetal variant angina before receiving
330 additional doses of sumatriptan, and should be monitored electrocardiographically if dosing is
331 resumed and similar symptoms recur. Similarly, patients who experience other symptoms or

332 signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud
333 syndrome following sumatriptan should be evaluated for atherosclerosis or predisposition to
334 vasospasm (see WARNINGS).

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

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

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

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

348 **Binding to Melanin-Containing Tissues:** In rats treated with a single subcutaneous dose
349 (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half-life of
350 radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or
351 its metabolites bind to the melanin of the eye. Comparable studies were not performed by the
352 intranasal route. Because there could be an accumulation in melanin-rich tissues over time, this
353 raises the possibility that sumatriptan could cause toxicity in these tissues after extended use.
354 However, no effects on the retina related to treatment with sumatriptan were noted in any of the
355 oral or subcutaneous toxicity studies. Although no systematic monitoring of ophthalmologic
356 function was undertaken in clinical trials, and no specific recommendations for ophthalmologic
357 monitoring are offered, prescribers should be aware of the possibility of long-term
358 ophthalmologic effects.

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

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

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

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

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

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

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

381 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** In
382 carcinogenicity studies, rats and mice were given sumatriptan by oral gavage (rats, 104 weeks) or
383 drinking water (mice, 78 weeks). Average exposures achieved in mice receiving the highest dose
384 (target dose of 160 mg/kg/day) were approximately 184 times the exposure attained in humans
385 after the maximum recommended single intranasal dose of 20 mg. The highest dose administered
386 to rats (160 mg/kg/day, reduced from 360 mg/kg/day during week 21) was approximately
387 78 times the maximum recommended single intranasal dose of 20 mg on a mg/m² basis. There
388 was no evidence of an increase in tumors in either species related to sumatriptan administration.
389 Local effects on nasal and respiratory tissue after chronic intranasal dosing in animals have not
390 been evaluated (see WARNINGS).

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

396 **Impairment of Fertility:** In a study in which male and female rats were dosed daily with
397 oral sumatriptan prior to and throughout the mating period, there was a treatment-related
398 decrease in fertility secondary to a decrease in mating in animals treated with 50 and
399 500 mg/kg/day. The highest no-effect dose for this finding was 5 mg/kg/day, or approximately
400 twice the maximum recommended single human intranasal dose of 20 mg on a mg/m² basis. It is
401 not clear whether the problem is associated with treatment of the males or females or both
402 combined. In a similar study by the subcutaneous route there was no evidence of impaired
403 fertility at 60 mg/kg/day, the maximum dose tested, which is equivalent to approximately
404 29 times the maximum recommended single human intranasal dose of 20 mg on a mg/m² basis.
405 Fertility studies, in which sumatriptan was administered by the intranasal route, were not
406 conducted.

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

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

415 **Embryolethality:** When given orally or intravenously to pregnant rabbits daily throughout
416 the period of organogenesis, sumatriptan caused embryolethality at doses at or close to those
417 producing maternal toxicity. In the oral studies this dose was 100 mg/kg/day, and in the
418 intravenous studies this dose was 2.0 mg/kg/day. The mechanism of the embryolethality is not
419 known. The highest no-effect dose for embryolethality by the oral route was 50 mg/kg/day,
420 which is approximately 48 times the maximum single recommended human intranasal dose of
421 20 mg on a mg/m² basis. By the intravenous route, the highest no-effect dose was
422 0.75 mg/kg/day, or approximately 0.7 times the maximum single recommended human intranasal
423 dose of 20 mg on a mg/m² basis.

424 The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at
425 12.5 mg/kg/day, the maximum dose tested, did not cause embryolethality. This dose is
426 approximately 6 times the maximum single recommended human intranasal dose of 20 mg on a
427 mg/m² basis. Additionally, in a study in rats given subcutaneous sumatriptan daily, prior to and
428 throughout pregnancy, at 60 mg/kg/day, the maximum dose tested, there was no evidence of
429 increased embryo/fetal lethality. This dose is equivalent to approximately 29 times the
430 maximum recommended single human intranasal dose of 20 mg on a mg/m² basis.

431 **Teratogenicity:** Oral treatment of pregnant rats with sumatriptan during the period of
432 organogenesis resulted in an increased incidence of blood vessel abnormalities (cervicothoracic
433 and umbilical) at doses of approximately 250 mg/kg/day or higher. The highest no-effect dose
434 was approximately 60 mg/kg/day, which is approximately 29 times the maximum single
435 recommended human intranasal dose of 20 mg on a mg/m² basis. Oral treatment of pregnant
436 rabbits with sumatriptan during the period of organogenesis resulted in an increased incidence of
437 cervicothoracic vascular and skeletal abnormalities. The highest no-effect dose for these effects
438 was 15 mg/kg/day, or approximately 14 times the maximum single recommended human
439 intranasal dose of 20 mg on a mg/m² basis.

440 A study in which rats were dosed daily with oral sumatriptan prior to and throughout gestation
441 demonstrated embryo/fetal toxicity (decreased body weight, decreased ossification, increased
442 incidence of rib variations) and an increased incidence of a syndrome of malformations (short
443 tail/short body and vertebral disorganization) at 500 mg/kg/day. The highest no-effect dose was
444 50 mg/kg/day, or approximately 24 times the maximum single recommended human intranasal
445 dose of 20 mg on a mg/m² basis. In a study in rats dosed daily with subcutaneous sumatriptan
446 prior to and throughout pregnancy, at a dose of 60 mg/kg/day, the maximum dose tested, there
447 was no evidence of teratogenicity. This dose is equivalent to approximately 29 times the
448 maximum recommended single human intranasal dose of 20 mg on a mg/m² basis.

449 **Pup Deaths:** Oral treatment of pregnant rats with sumatriptan during the period of
450 organogenesis resulted in a decrease in pup survival between birth and postnatal day 4 at doses
451 of approximately 250 mg/kg/day or higher. The highest no-effect dose for this effect was

452 approximately 60 mg/kg/day, or 29 times the maximum single recommended human intranasal
453 dose of 20 mg on a mg/m² basis.

454 Oral treatment of pregnant rats with sumatriptan from gestational day 17 through postnatal
455 day 21 demonstrated a decrease in pup survival measured at postnatal days 2, 4, and 20 at the
456 dose of 1,000 mg/kg/day. The highest no-effect dose for this finding was 100 mg/kg/day,
457 approximately 49 times the maximum single recommended human intranasal dose of 20 mg on a
458 mg/m² basis. In a similar study in rats by the subcutaneous route there was no increase in pup
459 death at 81 mg/kg/day, the highest dose tested, which is equivalent to 40 times the maximum
460 single recommended human intranasal dose of 20 mg on a mg/m² basis.

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

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

466 **Pediatric Use:** Safety and effectiveness of IMITREX Nasal Spray in pediatric patients under
467 18 years of age have not been established; therefore, IMITREX Nasal Spray is not recommended
468 for use in patients under 18 years of age.

469
470 Two controlled clinical trials evaluating sumatriptan nasal spray (5 to 20 mg) in pediatric
471 patients aged 12 to 17 years enrolled a total of 1,248 adolescent migraineurs who treated a single
472 attack. The studies did not establish the efficacy of sumatriptan nasal spray compared to placebo
473 in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were
474 similar in nature to those reported in clinical trials in adults.

475
476 Five controlled clinical trials (two single attack studies, three multiple attack studies) evaluating
477 oral sumatriptan (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701
478 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared
479 to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical
480 trials were similar in nature to those reported in clinical trials in adults. The frequency of all
481 adverse events in these patients appeared to be both dose- and age-dependent, with younger
482 patients reporting events more commonly than older adolescents.

483
484 Postmarketing experience documents that serious adverse events have occurred in the pediatric
485 population after use of subcutaneous sumatriptan, oral, and/or intranasal sumatriptan. These
486 reports include events similar in nature to those reported rarely in adults, including stroke, visual
487 loss, and death. A myocardial infarction has been reported in a 14-year-old male following the
488 use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Since
489 clinical data to determine the frequency of serious adverse events in pediatric patients who might
490 receive injectable, oral, or intranasal sumatriptan are not presently available, the use of
491 sumatriptan in patients aged younger than 18 years is not recommended.

492
493
494
495
496

497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

526 **Other Events Observed in Association With the Administration of IMITREX Nasal**
527 **Spray:** In the paragraphs that follow, the frequencies of less commonly reported adverse clinical
528 events are presented. Because the reports include events observed in open and uncontrolled
529 studies, the role of IMITREX Nasal Spray in their causation cannot be reliably determined.
530 Furthermore, variability associated with adverse event reporting, the terminology used to
531 describe adverse events, etc., limit the value of the quantitative frequency estimates provided.
532 Event frequencies are calculated as the number of patients who used IMITREX Nasal Spray (5,
533 10, or 20 mg in controlled and uncontrolled trials) and reported an event divided by the total
534 number of patients (n = 3,711) exposed to IMITREX Nasal Spray. All reported events are
535 included except those already listed in the previous table, those too general to be informative,
536 and those not reasonably associated with the use of the drug. Events are further classified within
537 body system categories and enumerated in order of decreasing frequency using the following
538 definitions: infrequent adverse events are those occurring in 1/100 to 1/1,000 patients and rare
539 adverse events are those occurring in fewer than 1/1,000 patients.

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

543 **Cardiovascular:** Infrequent were flushing and hypertension (see WARNINGS),
544 palpitations, tachycardia, changes in ECG, and arrhythmia (see WARNINGS and

545 PRECAUTIONS). Rare were abdominal aortic aneurysm, hypotension, bradycardia, pallor, and
546 phlebitis.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

583 **Cardiovascular:** Abnormal pulse, angina, atherosclerosis, cerebral ischemia,
584 cerebrovascular lesion, heart block, peripheral cyanosis, pulsating sensations, Raynaud

585 syndrome, thrombosis, transient myocardial ischemia, various transient ECG changes
586 (nonspecific ST or T wave changes, prolongation of PR or QTc intervals, sinus arrhythmia,
587 nonsustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats,
588 delayed activation of the right ventricle), and vasodilation.

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

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

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

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

602 **Hematological Disorders:** Anemia.

603 **Injection Site Reaction**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

648 **Psychiatry:** Panic disorder.

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

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

653 **Urogenital:** Acute renal failure.

654 **DRUG ABUSE AND DEPENDENCE**

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

658 **OVERDOSAGE**

659 In clinical trials, the highest single doses of IMITREX Nasal Spray administered without
660 significant adverse effects were 40 mg to 12 volunteers and 40 mg to 85 migraine patients, which

661 is twice the highest single recommended dose. In addition, 12 volunteers were administered a
662 total daily dose of 60 mg (20 mg 3 times daily) for 3.5 days without significant adverse events.

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

670 **DOSAGE AND ADMINISTRATION**

671 In controlled clinical trials, single doses of 5, 10, or 20 mg of IMITREX Nasal Spray
672 administered into 1 nostril were effective for the acute treatment of migraine in adults. A greater
673 proportion of patients had headache response following a 20-mg dose than following a 5- or
674 10-mg dose (see CLINICAL TRIALS). Individuals may vary in response to doses of IMITREX
675 Nasal Spray. The choice of dose should therefore be made on an individual basis, weighing the
676 possible benefit of the 20-mg dose with the potential for a greater risk of adverse events. A
677 10-mg dose may be achieved by the administration of a single 5-mg dose in each nostril. There is
678 evidence that doses above 20 mg do not provide a greater effect than 20 mg.

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

682 **HOW SUPPLIED**

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

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

687 **ANIMAL TOXICOLOGY**

688 **Corneal Opacities:** Dogs receiving oral sumatriptan developed corneal opacities and defects
689 in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day,
690 and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a
691 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses
692 were not established; however, the relative exposure at the lowest dose tested was approximately
693 5 times the human exposure after a 100-mg oral dose or 3 times the human exposure after a 6-mg
694 subcutaneous dose or 22 times the human exposure after a single 20-mg intranasal dose. There is
695 evidence of alterations in corneal appearance on the first day of intranasal dosing to dogs.
696 Changes were noted at the lowest dose tested, which was approximately 2 times the maximum
697 single human intranasal dose of 20 mg on a mg/m² basis.

698 **PATIENT INFORMATION**

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

700

701 **Information for the Patient**

702 **IMITREX[®] (sumatriptan) Nasal Spray**

703 Please read this leaflet carefully before you administer IMITREX Nasal Spray. This leaflet
704 provides a summary of the information available about your medicine. Please do not throw away
705 this leaflet until you have finished your medicine. You may need to read this leaflet again. This
706 leaflet does not contain all the information on IMITREX Nasal Spray. For further information or
707 advice, ask your doctor or pharmacist.

708 **Information About Your Medicine:**

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

721 ***1. The Purpose of Your Medicine:***

722 IMITREX Nasal Spray is intended to relieve your migraine, but not to prevent or reduce the
723 number of attacks you experience. Use IMITREX Nasal Spray only to treat an actual migraine
724 attack.

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

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

- 728 • Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant?
729 Are you using inadequate contraception? Are you breastfeeding?
- 730 • Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have
731 you had a heart attack?
- 732 • Do you have risk factors for heart disease (such as high blood pressure, high cholesterol,
733 obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal
734 or a male over 40)?
- 735 • Have you had a stroke, transient ischemic attacks (TIAs), or Raynaud syndrome?
- 736 • Do you have high blood pressure?

- 737 • Have you ever had to stop taking this or any other medicine because of an allergy or other
738 problems?
- 739 • Are you taking any other migraine medicines, including other 5-HT₁ agonists or any other
740 medicines containing ergotamine, dihydroergotamine, or methysergide?
- 741 • Are you taking any medicines for depression (monoamine oxidase inhibitors or selective
742 serotonin reuptake inhibitors [SSRIs])?
- 743 • Have you had, or do you have, any disease of the liver or kidney?
- 744 • Have you had, or do you have, epilepsy or seizures?
- 745 • Is this headache different from your usual migraine attacks?

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

748 **3. *The Use of IMITREX Nasal Spray During Pregnancy:***

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

752 **4. *How to Use IMITREX Nasal Spray:***

753 Before using IMITREX Nasal Spray, see the enclosed instruction pamphlet. For adults, the
754 usual dose is a single nasal spray administered into 1 nostril. If your headache comes back, a
755 second nasal spray may be administered anytime after 2 hours of administering the first spray.
756 For any attack where you have no response to the first nasal spray, do not take a second nasal
757 spray without first consulting with your doctor. Do not administer more than a total of 40 mg of
758 IMITREX Nasal Spray in any 24-hour period. The effects of long-term repeated use of
759 IMITREX Nasal Spray on the surfaces of the nose and throat have not been specifically studied.
760 The safety of treating an average of more than 4 headaches in a 30-day period has not been
761 established.

762 **5. *Side Effects to Watch for:***

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

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

779 **6. What to Do if an Overdose Is Taken:**

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

782 **7. Storing Your Medicine:**

783 Keep your medicine in a safe place where children cannot reach it. It may be harmful to
784 children. Store your medicine away from heat and light. Do not store at temperatures above 86°F
785 (30°C), or below 36°F (2°C). If your medicine has expired (the expiration date is printed on the
786 treatment pack), throw it away as instructed. If your doctor decides to stop your treatment, do not
787 keep any leftover medicine unless your doctor tells you to. Throw away your medicine as
788 instructed.

789

790



GlaxoSmithKline

791

792

GlaxoSmithKline

793

Research Triangle Park, NC 27709

794