

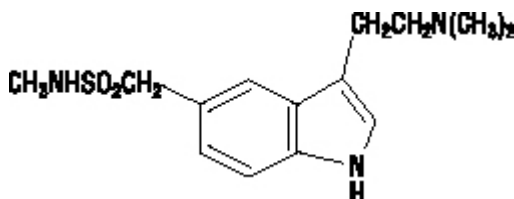
PRESCRIBING INFORMATION

IMITREX[®]

(sumatriptan)
Nasal Spray

DESCRIPTION

IMITREX (sumatriptan) Nasal Spray contains sumatriptan, a selective 5-hydroxytryptamine₁ 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 C₁₄H₂₁N₃O₂S, 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- μ 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-hydroxytryptamine₁ receptor subtype (probably a member of the 5-HT_{1D} family) having only a weak affinity for 5-HT_{1A}, 5-HT_{5A}, and 5-HT₇ receptors and no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT₂, 5-HT₃, or 5-HT₄ receptor subtypes or at alpha₁-, alpha₂-, or beta-adrenergic; dopamine₁; dopamine₂; muscarinic; or benzodiazepine receptors.

The vascular 5-HT₁ 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-HT₁ 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
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.

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%* (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)

128 *p<0.05 in comparison with placebo.

129 †p<0.05 in comparison with 10 mg.

130 ‡p<0.05 in comparison with 5 mg.

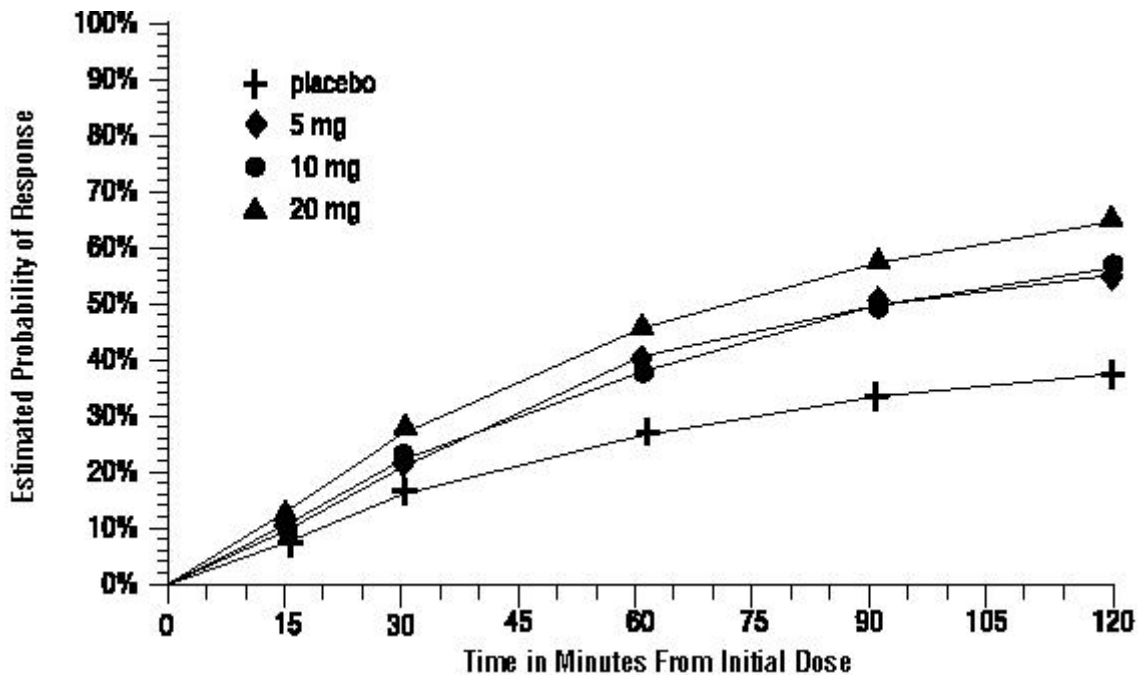
131 §Data are for attack 1 only of multiattack study for comparison.

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***
138



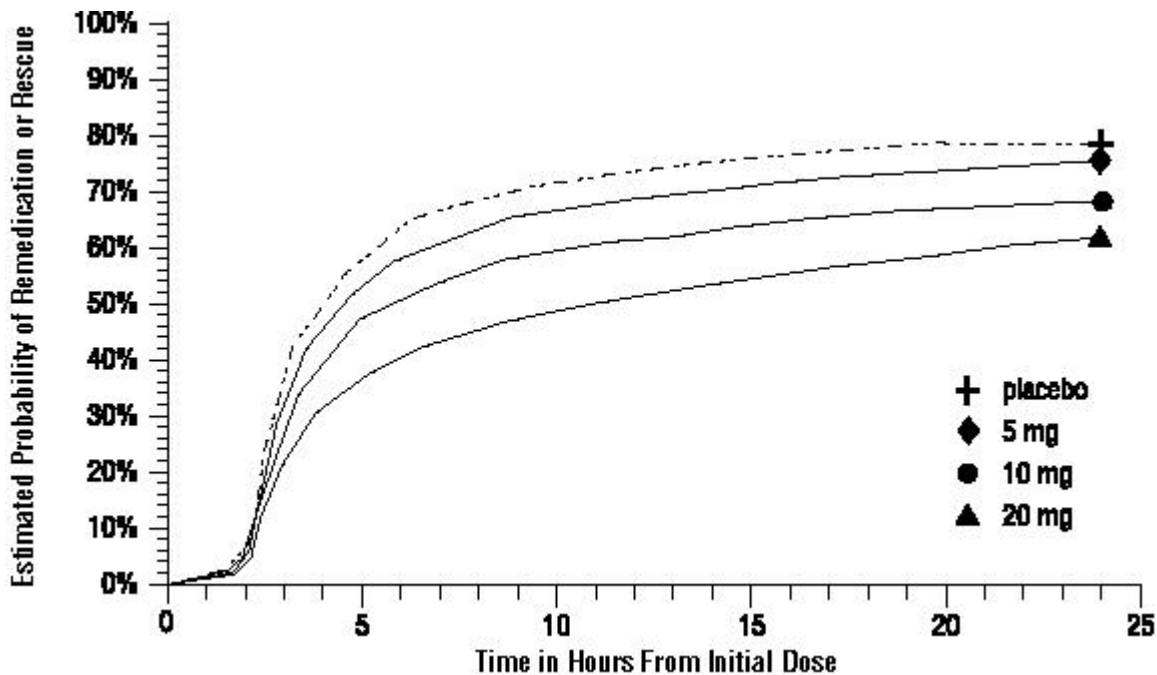
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140 * The figure shows the probability over time of obtaining headache response (no or mild
141 pain) following treatment with intranasal sumatriptan. The averages displayed are
142 based on pooled data from the 5 clinical controlled trials providing 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***
158



159 * Kaplan-Meier plot based on data obtained in the 3 clinical controlled trials providing
160 evidence of efficacy with patients not using additional treatments censored to 24 hours.
161 Plot also includes patients who had no response to the initial dose. No remedication
162 was allowed within 2 hours postdose.
163
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 and vasospastic forms of angina such as**
185 **the 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-HT₁ 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 **or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory**
212 **clinical evidence that the patient is reasonably free of coronary artery and ischemic**
213 **myocardial disease or other significant underlying cardiovascular disease. The sensitivity**
214 **of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to**
215 **coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the**
216 **patient's medical history or electrocardiographic investigations reveal findings indicative**

217 of, or consistent with, coronary artery vasospasm or myocardial ischemia, sumatriptan
218 should not be 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[®] (sumatriptan
236 succinate) Injection or IMITREX[®] (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:** The development of a potentially life-threatening serotonin syndrome
290 may occur with triptans, including treatment with IMITREX, particularly during combined use
291 with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake
292 inhibitors (SNRIs). If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine,
293 paroxetine, sertraline, fluvoxamine, citalopram, escitalopram) or SNRI (e.g., venlafaxine,
294 duloxetine) is clinically warranted, careful observation of the patient is advised, particularly
295 during treatment initiation and dose increases. Serotonin syndrome symptoms may include
296 mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g.,

297 tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia,
298 incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

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

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

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

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

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

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

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

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

338 **PRECAUTIONS**

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

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

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

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

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

364 **Binding to Melanin-Containing Tissues:** In rats treated with a single subcutaneous dose
365 (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half-life of
366 radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or
367 its metabolites bind to the melanin of the eye. Comparable studies were not performed by the
368 intranasal route. Because there could be an accumulation in melanin-rich tissues over time, this
369 raises the possibility that sumatriptan could cause toxicity in these tissues after extended use.
370 However, no effects on the retina related to treatment with sumatriptan were noted in any of the
371 oral or subcutaneous toxicity studies. Although no systematic monitoring of ophthalmologic
372 function was undertaken in clinical trials, and no specific recommendations for ophthalmologic
373 monitoring are offered, prescribers should be aware of the possibility of long-term
374 ophthalmologic effects.

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

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

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

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

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

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

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

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

401 **Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:*** In
402 carcinogenicity studies, rats and mice were given sumatriptan by oral gavage (rats, 104 weeks) or
403 drinking water (mice, 78 weeks). Average exposures achieved in mice receiving the highest dose
404 (target dose of 160 mg/kg/day) were approximately 184 times the exposure attained in humans
405 after the maximum recommended single intranasal dose of 20 mg. The highest dose administered
406 to rats (160 mg/kg/day, reduced from 360 mg/kg/day during week 21) was approximately
407 78 times the maximum recommended single intranasal dose of 20 mg on a mg/m² basis. There
408 was no evidence of an increase in tumors in either species related to sumatriptan administration.
409 Local effects on nasal and respiratory tissue after chronic intranasal dosing in animals have not
410 been evaluated (see WARNINGS).

411 ***Mutagenesis:*** Sumatriptan was not mutagenic in the presence or absence of metabolic
412 activation when tested in 2 gene mutation assays (the Ames test and the in vitro mammalian
413 Chinese hamster V79/HGPRT assay). In 2 cytogenetics assays (the in vitro human lymphocyte

414 assay and the in vivo rat micronucleus assay) sumatriptan was not associated with clastogenic
415 activity.

416 **Impairment of Fertility:** In a study in which male and female rats were dosed daily with
417 oral sumatriptan prior to and throughout the mating period, there was a treatment-related
418 decrease in fertility secondary to a decrease in mating in animals treated with 50 and
419 500 mg/kg/day. The highest no-effect dose for this finding was 5 mg/kg/day, or approximately
420 twice the maximum recommended single human intranasal dose of 20 mg on a mg/m² basis. It is
421 not clear whether the problem is associated with treatment of the males or females or both
422 combined. In a similar study by the subcutaneous route there was no evidence of impaired
423 fertility at 60 mg/kg/day, the maximum dose tested, which is equivalent to approximately
424 29 times the maximum recommended single human intranasal dose of 20 mg on a mg/m² basis.
425 Fertility studies, in which sumatriptan was administered by the intranasal route, were not
426 conducted.

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

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

435 **Embryoletality:** When given orally or intravenously to pregnant rabbits daily throughout
436 the period of organogenesis, sumatriptan caused embryoletality at doses at or close to those
437 producing maternal toxicity. In the oral studies this dose was 100 mg/kg/day, and in the
438 intravenous studies this dose was 2.0 mg/kg/day. The mechanism of the embryoletality is not
439 known. The highest no-effect dose for embryoletality by the oral route was 50 mg/kg/day,
440 which is approximately 48 times the maximum single recommended human intranasal dose of
441 20 mg on a mg/m² basis. By the intravenous route, the highest no-effect dose was
442 0.75 mg/kg/day, or approximately 0.7 times the maximum single recommended human intranasal
443 dose of 20 mg on a mg/m² basis.

444 The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at
445 12.5 mg/kg/day, the maximum dose tested, did not cause embryoletality. This dose is
446 approximately 6 times the maximum single recommended human intranasal dose of 20 mg on a
447 mg/m² basis. Additionally, in a study in rats given subcutaneous sumatriptan daily, prior to and
448 throughout pregnancy, at 60 mg/kg/day, the maximum dose tested, there was no evidence of
449 increased embryo/fetal lethality. This dose is equivalent to approximately 29 times the
450 maximum recommended single human intranasal dose of 20 mg on a mg/m² basis.

451 **Teratogenicity:** Oral treatment of pregnant rats with sumatriptan during the period of
452 organogenesis resulted in an increased incidence of blood vessel abnormalities (cervicothoracic
453 and umbilical) at doses of approximately 250 mg/kg/day or higher. The highest no-effect dose

454 was approximately 60 mg/kg/day, which is approximately 29 times the maximum single
455 recommended human intranasal dose of 20 mg on a mg/m² basis. Oral treatment of pregnant
456 rabbits with sumatriptan during the period of organogenesis resulted in an increased incidence of
457 cervicothoracic vascular and skeletal abnormalities. The highest no-effect dose for these effects
458 was 15 mg/kg/day, or approximately 14 times the maximum single recommended human
459 intranasal dose of 20 mg on a mg/m² basis.

460 A study in which rats were dosed daily with oral sumatriptan prior to and throughout gestation
461 demonstrated embryo/fetal toxicity (decreased body weight, decreased ossification, increased
462 incidence of rib variations) and an increased incidence of a syndrome of malformations (short
463 tail/short body and vertebral disorganization) at 500 mg/kg/day. The highest no-effect dose was
464 50 mg/kg/day, or approximately 24 times the maximum single recommended human intranasal
465 dose of 20 mg on a mg/m² basis. In a study in rats dosed daily with subcutaneous sumatriptan
466 prior to and throughout pregnancy, at a dose of 60 mg/kg/day, the maximum dose tested, there
467 was no evidence of teratogenicity. This dose is equivalent to approximately 29 times the
468 maximum recommended single human intranasal dose of 20 mg on a mg/m² basis.

469 **Pup Deaths:** Oral treatment of pregnant rats with sumatriptan during the period of
470 organogenesis resulted in a decrease in pup survival between birth and postnatal day 4 at doses
471 of approximately 250 mg/kg/day or higher. The highest no-effect dose for this effect was
472 approximately 60 mg/kg/day, or 29 times the maximum single recommended human intranasal
473 dose of 20 mg on a mg/m² basis.

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

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

484 **Nursing Mothers:** Sumatriptan is excreted in human breast milk following subcutaneous
485 administration. Infant exposure to sumatriptan can be minimized by avoiding breastfeeding for
486 12 hours after treatment with IMITREX Nasal Spray.

487 **Pediatric Use:** Safety and effectiveness of IMITREX Nasal Spray in pediatric patients under
488 18 years of age have not been established; therefore, IMITREX Nasal Spray is not recommended
489 for use in patients under 18 years of age.

490 Two controlled clinical trials evaluating sumatriptan nasal spray (5 to 20 mg) in pediatric
491 patients aged 12 to 17 years enrolled a total of 1,248 adolescent migraineurs who treated a single
492 attack. The studies did not establish the efficacy of sumatriptan nasal spray compared to placebo

493 in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were
494 similar in nature to those reported in clinical trials in adults.

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

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

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

513 **ADVERSE REACTIONS**

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

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

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

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

532

533 **Table 2. Treatment-Emergent Adverse Events Reported by at Least 1% of Patients in**
534 **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%

535

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

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

542 **Other Events Observed in Association With the Administration of IMITREX Nasal**
543 **Spray:** In the paragraphs that follow, the frequencies of less commonly reported adverse clinical
544 events are presented. Because the reports include events observed in open and uncontrolled
545 studies, the role of IMITREX Nasal Spray in their causation cannot be reliably determined.
546 Furthermore, variability associated with adverse event reporting, the terminology used to
547 describe adverse events, etc., limit the value of the quantitative frequency estimates provided.
548 Event frequencies are calculated as the number of patients who used IMITREX Nasal Spray (5,
549 10, or 20 mg in controlled and uncontrolled trials) and reported an event divided by the total
550 number of patients (N = 3,711) exposed to IMITREX Nasal Spray. All reported events are
551 included except those already listed in the previous table, those too general to be informative,
552 and those not reasonably associated with the use of the drug. Events are further classified within
553 body system categories and enumerated in order of decreasing frequency using the following
554 definitions: infrequent adverse events are those occurring in 1/100 to 1/1,000 patients and rare
555 adverse events are those occurring in fewer than 1/1,000 patients.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

618 **Hematological Disorders:** Anemia.

619 **Injection Site Reaction**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

664 **Psychiatry:** Panic disorder.

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

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

669 **Urogenital:** Acute renal failure.

670 DRUG ABUSE AND DEPENDENCE

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

674 **OVERDOSAGE**

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

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

686 **DOSAGE AND ADMINISTRATION**

687 In controlled clinical trials, single doses of 5, 10, or 20 mg of IMITREX Nasal Spray
688 administered into 1 nostril were effective for the acute treatment of migraine in adults. A greater
689 proportion of patients had headache response following a 20-mg dose than following a 5- or
690 10-mg dose (see CLINICAL TRIALS). Individuals may vary in response to doses of IMITREX
691 Nasal Spray. The choice of dose should therefore be made on an individual basis, weighing the
692 possible benefit of the 20-mg dose with the potential for a greater risk of adverse events. A
693 10-mg dose may be achieved by the administration of a single 5-mg dose in each nostril. There is
694 evidence that doses above 20 mg do not provide a greater effect than 20 mg.

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

698 **HOW SUPPLIED**

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

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

703 **ANIMAL TOXICOLOGY**

704 **Corneal Opacities:** Dogs receiving oral sumatriptan developed corneal opacities and defects
705 in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day,
706 and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a
707 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses
708 were not established; however, the relative exposure at the lowest dose tested was approximately
709 5 times the human exposure after a 100-mg oral dose or 3 times the human exposure after a 6-mg
710 subcutaneous dose or 22 times the human exposure after a single 20-mg intranasal dose. There is
711 evidence of alterations in corneal appearance on the first day of intranasal dosing to dogs.

712 Changes were noted at the lowest dose tested, which was approximately 2 times the maximum
713 single human intranasal dose of 20 mg on a mg/m² basis.

714 **PATIENT INFORMATION**

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

716

717

718

Information for the Patient **IMITREX[®]* (sumatriptan) Nasal Spray**

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

724 **Information About Your Medicine:**

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

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

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

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

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

- 744 • Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant?
745 Are you using inadequate contraception? Are you breastfeeding?
- 746 • Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have
747 you had a heart attack?
- 748 • Do you have risk factors for heart disease (such as high blood pressure, high cholesterol,
749 obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal
750 or a male over 40)?

- 751 • Have you had a stroke, transient ischemic attacks (TIAs), or Raynaud syndrome?
752 • Do you have high blood pressure?
753 • Have you ever had to stop taking this or any other medicine because of an allergy or other
754 problems?
755 • Are you taking any other migraine medicines, including other 5-HT₁ agonists or any other
756 medicines containing ergotamine, dihydroergotamine, or methysergide?
757 • Are you taking any medicine for depression or other disorders such as monoamine oxidase
758 inhibitors, selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine
759 reuptake inhibitors (SNRIs)? Common SSRIs are citalopram HBr (CELEXA[®]), escitalopram
760 oxalate (LEXAPRO[®]), paroxetine (PAXIL[®]), fluoxetine (PROZAC[®]/SARAFEM[®]),
761 olanzapine/fluoxetine (SYMBYAX[®]), sertraline (ZOLOFT[®]), and fluvoxamine. Common
762 SNRIs are duloxetine (CYMBALTA[®]) and venlafaxine (EFFEXOR[®])*.
763 • Have you had, or do you have, any disease of the liver or kidney?
764 • Have you had, or do you have, epilepsy or seizures?
765 • Is this headache different from your usual migraine attacks?

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

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

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

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

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

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

- 783 • Some patients experience pain or tightness in the chest or throat when using IMITREX Nasal
784 Spray. If this happens to you, then discuss it with your doctor before using any more
785 IMITREX Nasal Spray. If the chest pain is severe or does not go away, call your doctor
786 immediately.
787 • If you have sudden and/or severe abdominal pain following IMITREX Nasal Spray, call your
788 doctor immediately.
789 • Some people may have a reaction called serotonin syndrome when they use certain types of
790 antidepressants, SSRIs or SNRIs, while taking IMITREX Nasal Spray. Symptoms may

791 include confusion, hallucinations, fast heartbeat, feeling faint, fever, sweating, muscle spasm,
792 difficulty walking, and/or diarrhea. Call your doctor immediately if you have any of these
793 symptoms after taking IMITREX Nasal Spray.

794 • Shortness of breath; wheeziness; heart throbbing; swelling of eyelids, face, or lips; or a skin
795 rash, skin lumps, or hives happens rarely. If it happens to you, then tell your doctor
796 immediately. Do not take any more IMITREX Nasal Spray unless your doctor tells you to do
797 so.

798 • Some people may have feelings of tingling, heat, flushing (redness of face lasting a short
799 time), heaviness or pressure after treatment with IMITREX Nasal Spray. A few people may
800 feel drowsy, dizzy, tired, sick, or may experience nasal irritation. Tell your doctor of these
801 symptoms at your next visit.

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

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

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

807 **7. Storing Your Medicine:**

808 Keep your medicine in a safe place where children cannot reach it. It may be harmful to
809 children. Store your medicine away from heat and light. Do not store at temperatures above 86°F
810 (30°C), or below 36°F (2°C). If your medicine has expired (the expiration date is printed on the
811 treatment pack), throw it away as instructed. If your doctor decides to stop your treatment, do not
812 keep any leftover medicine unless your doctor tells you to. Throw away your medicine as
813 instructed.

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816 are trademarks of their respective owners and are not trademarks of GlaxoSmithKline. The
817 makers of these brands are not affiliated with and do not endorse GlaxoSmithKline or its
818 products.

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