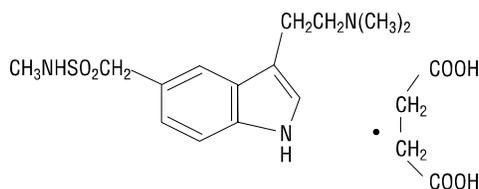


PRESCRIBING INFORMATION**1**
2 **IMITREX[®]**
3 **(sumatriptan succinate)**
4 **Injection****5**
6 **For Subcutaneous Use Only.****7** **DESCRIPTION**

8 IMITREX (sumatriptan succinate) Injection is a selective 5-hydroxytryptamine₁ receptor
9 subtype agonist. Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino)ethyl]-
10 N-methyl-indole-5-methanesulfonamide succinate (1:1), and it has the following structure:



12 The empirical formula is C₁₄H₂₁N₃O₂S•C₄H₆O₄, representing a molecular weight of 413.5.

13 Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in
14 saline.

15 IMITREX Injection is a clear, colorless to pale yellow, sterile, nonpyrogenic solution for
16 subcutaneous injection. Each 0.5 mL of IMITREX Injection 8 mg/mL solution contains 4 mg of
17 sumatriptan (base) as the succinate salt and 3.8 mg of sodium chloride, USP in Water for
18 Injection, USP. Each 0.5 mL of IMITREX Injection 12 mg/mL solution contains 6 mg of
19 sumatriptan (base) as the succinate salt and 3.5 mg of sodium chloride, USP in Water for
20 Injection, USP. The pH range of both solutions is approximately 4.2 to 5.3. The osmolality of
21 both injections is 291 mOsmol.
22
23

24 **CLINICAL PHARMACOLOGY**

25 **Mechanism of Action:** Sumatriptan has been demonstrated to be a selective agonist for a
26 vascular 5-hydroxytryptamine₁ receptor subtype (probably a member of the 5-HT_{1D} family) with
27 no significant affinity (as measured using standard radioligand binding assays) or
28 pharmacological activity at 5-HT₂, 5-HT₃ receptor subtypes or at alpha₁-, alpha₂-, or
29 beta-adrenergic; dopamine₁; dopamine₂; muscarinic; or benzodiazepine receptors.

30 The vascular 5-HT₁ receptor subtype to which sumatriptan binds selectively, and through
31 which it presumably exerts its antimigrainous effect, has been shown to be present on cranial
32 arteries in both dog and primate, on the human basilar artery, and in the vasculature of the
33 isolated dura mater of humans. In these tissues, sumatriptan activates this receptor to cause

34 vasoconstriction, an action in humans correlating with the relief of migraine and cluster
35 headache. In the anesthetized dog, sumatriptan selectively reduces the carotid arterial blood flow
36 with little or no effect on arterial blood pressure or total peripheral resistance. In the cat,
37 sumatriptan selectively constricts the carotid arteriovenous anastomoses while having little effect
38 on blood flow or resistance in cerebral or extracerebral tissues.

39 **Corneal Opacities:** Dogs receiving oral sumatriptan developed corneal opacities and defects
40 in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day,
41 and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a
42 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses
43 were not established; however, the relative exposure at the lowest dose tested was approximately
44 5 times the human exposure after a 100-mg oral dose or 3 times the human exposure after a 6-mg
45 subcutaneous dose.

46 **Melanin Binding:** In rats with a single subcutaneous dose (0.5 mg/kg) of radiolabeled
47 sumatriptan, the elimination half-life of radioactivity from the eye was 15 days, suggesting that
48 sumatriptan and its metabolites bind to the melanin of the eye. The clinical significance of this
49 binding is unknown.

50 **Pharmacokinetics:** Pharmacokinetic parameters following a 6-mg subcutaneous injection into
51 the deltoid area of the arm in 9 males (mean age, 33 years; mean weight, 77 kg) were systemic
52 clearance: $1,194 \pm 149$ mL/min (mean \pm S.D.), distribution half-life: 15 ± 2 minutes, terminal
53 half-life: 115 ± 19 minutes, and volume of distribution central compartment: 50 ± 8 liters. Of this
54 dose, $22\% \pm 4\%$ was excreted in the urine as unchanged sumatriptan and $38\% \pm 7\%$ as the indole
55 acetic acid metabolite.

56 After a single 6-mg subcutaneous manual injection into the deltoid area of the arm in 18
57 healthy males (age, 24 ± 6 years; weight, 70 kg), the maximum serum concentration (C_{\max}) was
58 (mean \pm standard deviation) 74 ± 15 ng/mL and the time to peak concentration (T_{\max}) was
59 12 minutes after injection (range, 5 to 20 minutes). In this study, the same dose injected
60 subcutaneously in the thigh gave a C_{\max} of 61 ± 15 ng/mL by manual injection versus
61 52 ± 15 ng/mL by autoinjector techniques. The T_{\max} or amount absorbed was not significantly
62 altered by either the site or technique of injection.

63 The bioavailability of sumatriptan via subcutaneous site injection to 18 healthy male subjects
64 was $97\% \pm 16\%$ of that obtained following intravenous injection. Protein binding, determined by
65 equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL, is low, approximately
66 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been
67 evaluated.

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

71 **Hepatic Impairment:** The effect of hepatic disease on the pharmacokinetics of
72 subcutaneously and orally administered sumatriptan has been evaluated. There were no
73 statistically significant differences in the pharmacokinetics of subcutaneously administered
74 sumatriptan in hepatically impaired patients compared to healthy controls. However, the liver
75 plays an important role in the presystemic clearance of orally administered sumatriptan.
76 Accordingly, the bioavailability of sumatriptan following oral administration may be markedly
77 increased in patients with liver disease. In 1 small study of hepatically impaired patients (n = 8)
78 matched for sex, age, and weight with healthy subjects, the hepatically impaired patients had an
79 approximately 70% increase in AUC and C_{\max} and a T_{\max} 40 minutes earlier compared to the
80 healthy subjects.

81 **Age:** The pharmacokinetics of sumatriptan in the elderly (mean age, 72 years, 2 males and
82 4 females) and in patients with migraine (mean age, 38 years, 25 males and 155 females) were
83 similar to that in healthy male subjects (mean age, 30 years) (see PRECAUTIONS: Geriatric
84 Use).

85 **Race:** The systemic clearance and C_{\max} of sumatriptan were similar in black (N = 34) and
86 Caucasian (N = 38) healthy male subjects.

87 **Drug Interactions: Monoamine Oxidase Inhibitors:** In vitro studies with human
88 microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO),
89 predominantly the A isoenzyme. In a study of 14 healthy females, pretreatment with MAO-A
90 inhibitor decreased the clearance of sumatriptan. Under the conditions of this experiment, the
91 result was a 2-fold increase in the area under the sumatriptan plasma concentration x time curve
92 (AUC), corresponding to a 40% increase in elimination half-life. No significant effect was seen
93 with an MAO-B inhibitor.

94 **Pharmacodynamics:**

95 **Typical Physiologic Responses:**

96 **Blood Pressure:** (see WARNINGS: Increase in Blood Pressure)

97 **Peripheral (small) Arteries:** In healthy volunteers (N = 18), a study evaluating the effects
98 of sumatriptan on peripheral (small vessel) arterial reactivity failed to detect a clinically
99 significant increase in peripheral resistance.

100 **Heart Rate:** Transient increases in blood pressure observed in some patients in clinical
101 studies carried out during sumatriptan's development as a treatment for migraine were not
102 accompanied by any clinically significant changes in heart rate.

103 **Respiratory Rate:** Experience gained during the clinical development of sumatriptan as a
104 treatment for migraine failed to detect an effect of the drug on respiratory rate.

105 **CLINICAL TRIALS**

106 **Migraine:** In US controlled clinical trials enrolling more than 1,000 patients during migraine
107 attacks who were experiencing moderate or severe pain and 1 or more of the symptoms
108 enumerated in Table 2, onset of relief began as early as 10 minutes following a 6-mg IMITREX

109 Injection. Smaller doses of sumatriptan may also prove effective, although the proportion of
 110 patients obtaining adequate relief is decreased and the latency to that relief is greater.

111 In 1 well-controlled study where placebo (n = 62) was compared to 6 different doses of
 112 IMITREX Injection (n = 30 each group) in a single-attack, parallel-group design, the dose
 113 response relationship was found to be as shown in Table 1.

114

115 **Table 1. Dose Response Relationship for Efficacy**

IMITREX Dose (mg)	% Patients With Relief* at 10 Minutes	% Patients With Relief* at 30 Minutes	% Patients With Relief* at 1 Hour	% Patients With Relief* at 2 Hours	Adverse Events Incidence (%)
Placebo	5	15	24	21	55
1	10	40	43	40	63
2	7	23	57	43	63
3	17	47	57	60	77
4	13	37	50	57	80
6	10	63	73	70	83
8	23	57	80	83	93

* Relief is defined as the reduction of moderate or severe pain to no or mild pain after dosing
 without use of rescue medication.

116

117 In 2 US well-controlled clinical trials in 1,104 migraine patients with moderate or severe
 118 migraine pain, the onset of relief was rapid (less than 10 minutes) with IMITREX Injection 6 mg.
 119 Headache relief, as evidenced by a reduction in pain from severe or moderately severe to mild or
 120 no headache, was achieved in 70% of the patients within 1 hour of a single 6-mg subcutaneous
 121 dose of IMITREX Injection. Headache relief was achieved in approximately 82% of patients
 122 within 2 hours, and 65% of all patients were pain free within 2 hours.

123 Table 2 shows the 1- and 2-hour efficacy results for IMITREX Injection 6 mg.

124

125 **Table 2. Efficacy Data From US Phase III Trials**

1-Hour Data	Study 1		Study 2	
	Placebo (n = 190)	IMITREX 6 mg (n = 384)	Placebo (n = 180)	IMITREX 6 mg (n = 350)
Patients with pain relief (grade 0/1)	18%	70% [*]	26%	70% [*]
Patients with no pain	5%	48% [*]	13%	49% [*]
Patients without nausea	48%	73% [*]	50%	73% [*]
Patients without photophobia	23%	56% [*]	25%	58% [*]
Patients with little or no clinical disability [§]	34%	76% [*]	34%	76% [*]
2-Hour Data	Study 1		Study 2	
	Placebo [†]	IMITREX 6 mg [‡]	Placebo [†]	IMITREX 6 mg [‡]
Patients with pain relief (grade 0/1)	31%	81% [*]	39%	82% [*]
Patients with no pain	11%	63% [*]	19%	65% [*]
Patients without nausea	56%	82% [*]	63%	81% [*]
Patients without photophobia	31%	72% [*]	35%	71% [*]
Patients with little or no clinical disability [§]	42%	85% [*]	49%	84% [*]

^{*} p<0.05 versus placebo.

[†] Includes patients that may have received an additional placebo injection 1 hour after the initial injection.

[‡] Includes patients that may have received an additional 6 mg of IMITREX Injection 1 hour after the initial injection.

[§] A successful outcome in terms of clinical disability was defined prospectively as ability to work mildly impaired or ability to work and function normally.

126

127 IMITREX Injection also relieved photophobia, phonophobia (sound sensitivity), nausea, and
128 vomiting associated with migraine attacks. Similar efficacy was seen when patients
129 self-administered IMITREX Injection using an autoinjector.

130 The efficacy of IMITREX Injection is unaffected by whether or not migraine is associated
131 with aura, duration of attack, gender or age of the patient, or concomitant use of common
132 migraine prophylactic drugs (e.g., beta-blockers).

133 **Cluster Headache:** The efficacy of IMITREX Injection in the acute treatment of cluster
134 headache was demonstrated in 2 randomized, double-blind, placebo-controlled, 2-period
135 crossover trials. Patients age 21 to 65 were enrolled and were instructed to treat a moderate to
136 very severe headache within 10 minutes of onset. Headache relief was defined as a reduction in

137 headache severity to mild or no pain. In both trials, the proportion of individuals gaining relief at
 138 10 or 15 minutes was significantly greater among patients receiving 6 mg of IMITREX Injection
 139 compared to those who received placebo (see Table 3). One study evaluated a 12-mg dose; there
 140 was no statistically significant difference in outcome between patients randomized to the 6- and
 141 12-mg doses.

142

143 **Table 3. Efficacy Data From the Pivotal Cluster Headache Studies**

	Study 1		Study 2	
	Placebo (n = 39)	IMITREX 6 mg (n = 39)	Placebo (n = 88)	IMITREX 6 mg (n = 92)
Patients with pain relief (no/mild)				
5 minutes postinjection	8%	21%	7%	23%*
10 minutes postinjection	10%	49%*	25%	49%*
15 minutes postinjection	26%	74%*	35%	75%*

* p<0.05.

(n = Number of headaches treated.)

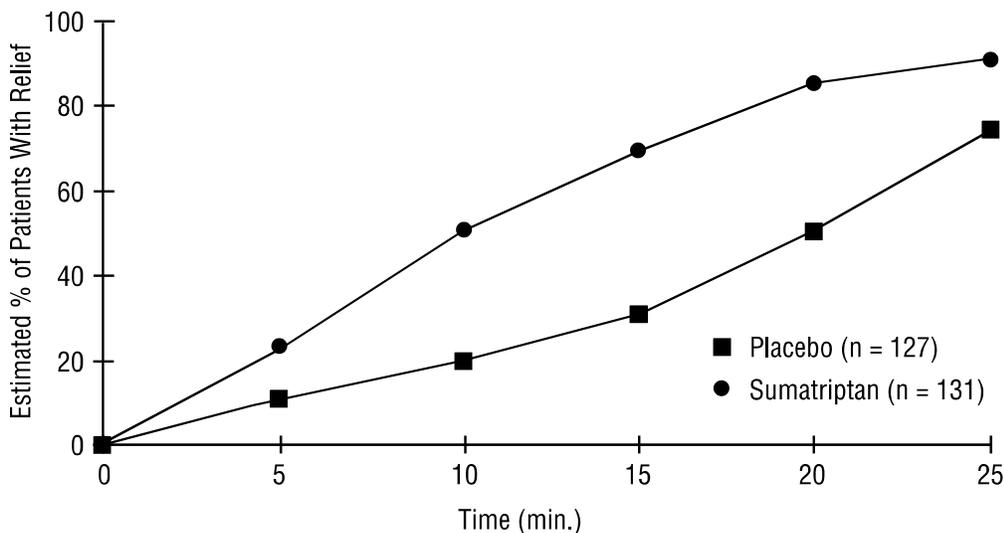
144

145 The Kaplan-Meier (product limit) Survivorship Plot (Figure 1) provides an estimate of the
 146 cumulative probability of a patient with a cluster headache obtaining relief after being treated
 147 with either sumatriptan or placebo.

148

149 **Figure 1. Time to Relief From Time of Injection***

150



151

152 *Patients taking rescue medication were censored at 15 minutes.

153

154 The plot was constructed with data from patients who either experienced relief or did not
155 require (request) rescue medication within a period of 2 hours following treatment. As a
156 consequence, the data in the plot are derived from only a subset of the 258 headaches treated
157 (rescue medication was required in 52 of the 127 placebo-treated headaches and 18 of the 131
158 sumatriptan-treated headaches).

159 Other data suggest that sumatriptan treatment is not associated with an increase in early
160 recurrence of headache, and that treatment with sumatriptan has little effect on the incidence of
161 latter-occurring headaches (i.e., those occurring after 2, but before 18 or 24 hours).

162 **INDICATIONS AND USAGE**

163 IMITREX Injection is indicated for 1) the acute treatment of migraine attacks with or without
164 aura and 2) the acute treatment of cluster headache episodes.

165 IMITREX Injection is not for use in the management of hemiplegic or basilar migraine (see
166 CONTRAINDICATIONS).

167 **CONTRAINDICATIONS**

168 **IMITREX Injection should not be given intravenously because of its potential to cause**
169 **coronary vasospasm.**

170 **IMITREX Injection should not be given to patients with history, symptoms, or signs of**
171 **ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients**
172 **with other significant underlying cardiovascular diseases should not receive IMITREX**
173 **Injection. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of**
174 **any type (e.g., stable angina of effort and vasospastic forms of angina such as the**
175 **Prinzmetal variant), all forms of myocardial infarction, and silent myocardial ischemia.**
176 **Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as**
177 **transient ischemic attacks. Peripheral vascular disease includes, but is not limited to,**
178 **ischemic bowel disease (see WARNINGS: Other Vasospasm-Related Events and**
179 **WARNINGS: Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac**
180 **Events).**

181 **Because IMITREX Injection may increase blood pressure, it should not be given to**
182 **patients with uncontrolled hypertension.**

183 **IMITREX Injection and any ergotamine-containing or ergot-type medication (like**
184 **dihydroergotamine or methysergide) should not be used within 24 hours of each other, nor**
185 **should IMITREX Injection and another 5-HT₁ agonist.**

186 **IMITREX Injection should not be administered to patients with hemiplegic or basilar**
187 **migraine.**

188 **IMITREX Injection is contraindicated in patients with hypersensitivity to sumatriptan**
189 **or any of its components.**

190 **IMITREX Injection is contraindicated in patients with severe hepatic impairment.**

191 **WARNINGS**

192 **IMITREX Injection should only be used where a clear diagnosis of migraine or cluster**
193 **headache has been established. The prescriber should be aware that cluster headache**
194 **patients often possess one or more predictive risk factors for coronary artery disease**
195 **(CAD).**

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

210 **For patients with risk factors predictive of CAD who are determined to have a**
211 **satisfactory cardiovascular evaluation, it is strongly recommended that administration of**
212 **the first dose of sumatriptan injection take place in the setting of a physician's office or**
213 **similar medically staffed and equipped facility. Because cardiac ischemia can occur in the**
214 **absence of clinical symptoms, consideration should be given to obtaining on the first**
215 **occasion of use an electrocardiogram (ECG) during the interval immediately following**
216 **IMITREX Injection, in these patients with risk factors.**

217 **It is recommended that patients who are intermittent long-term users of sumatriptan**
218 **and who have or acquire risk factors predictive of CAD, as described above, undergo**
219 **periodic interval cardiovascular evaluation as they continue to use sumatriptan. In**
220 **considering this recommendation for periodic cardiovascular evaluation, it is noted that**
221 **patients with cluster headache are predominantly male and over 40 years of age, which are**
222 **risk factors for CAD.**

223 **The systematic approach described above is intended to reduce the likelihood that patients**
224 **with unrecognized cardiovascular disease will be inadvertently exposed to sumatriptan.**

225 **Drug-Associated Cardiac Events and Fatalities:** Serious adverse cardiac events,
226 including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death
227 have been reported within a few hours following the administration of IMITREX Injection or

228 IMITREX[®] (sumatriptan succinate) Tablets. Considering the extent of use of sumatriptan in
229 patients with migraine, the incidence of these events is extremely low.

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

235 **Premarketing Experience With Sumatriptan:** Among the more than 1,900 patients with
236 migraine who participated in premarketing controlled clinical trials of subcutaneous sumatriptan,
237 there were 8 patients who sustained clinical events during or shortly after receiving sumatriptan
238 that may have reflected coronary artery vasospasm. Six of these 8 patients had ECG changes
239 consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of
240 these 8 patients, 4 had either findings suggestive of CAD or risk factors predictive of CAD prior
241 to study enrollment.

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

246 Among approximately 4,000 patients with migraine who participated in premarketing
247 controlled and uncontrolled clinical trials of sumatriptan nasal spray, 1 patient experienced an
248 asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.

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

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

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

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

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

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

287 **Concomitant Drug Use:** In patients taking MAO-A inhibitors, sumatriptan plasma levels
288 attained after treatment with recommended doses are nearly double those obtained under other
289 conditions. Accordingly, the coadministration of sumatriptan and an MAO-A inhibitor is not
290 generally recommended. If such therapy is clinically warranted, however, suitable dose
291 adjustment and appropriate observation of the patient is advised (see CLINICAL
292 PHARMACOLOGY: Drug Interactions: *Monoamine Oxidase Inhibitors*).

293 **Use in Women of Childbearing Potential:** (see PRECAUTIONS: Pregnancy)

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

298 PRECAUTIONS

299 **General:** Chest, jaw, or neck tightness is relatively common after administration of IMITREX
300 Injection. Chest discomfort and jaw or neck tightness have been reported following use of
301 IMITREX Tablets and have also been reported infrequently following the administration of
302 IMITREX[®] (sumatriptan) Nasal Spray. Only rarely have these symptoms been associated with

303 ischemic ECG changes. However, because sumatriptan may cause coronary artery vasospasm,
304 patients who experience signs or symptoms suggestive of angina following sumatriptan should be
305 evaluated for the presence of CAD or a predisposition to Prinzmetal variant angina before
306 receiving additional doses of sumatriptan and should be monitored electrocardiographically if
307 dosing is resumed and similar symptoms recur. Similarly, patients who experience other
308 symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or
309 Raynaud syndrome, following sumatriptan should be evaluated for atherosclerosis or
310 predisposition to vasospasm (see WARNINGS: Risk of Myocardial Ischemia and/or Infarction
311 and Other Adverse Cardiac Events and WARNINGS: Other Vasospasm-Related Events).

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

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

317 Care should be taken to exclude other potentially serious neurologic conditions before treating
318 headache in patients not previously diagnosed with migraine or cluster headache or who
319 experience a headache that is atypical for them. There have been rare reports where patients
320 received sumatriptan for severe headaches that were subsequently shown to have been secondary
321 to an evolving neurologic lesion (see WARNINGS: Drug-Associated Cerebrovascular Events
322 and Fatalities). For a given attack, if a patient does not respond to the first dose of sumatriptan,
323 the diagnosis of migraine or cluster headache should be reconsidered before administration of a
324 second dose.

325 **Binding to Melanin-Containing Tissues:** Because sumatriptan binds to melanin, it could
326 accumulate in melanin-rich tissues (such as the eye) over time. This raises the possibility that
327 sumatriptan could cause toxicity in these tissues after extended use. However, no effects on the
328 retina related to treatment with sumatriptan were noted in any of the toxicity studies. Although no
329 systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no
330 specific recommendations for ophthalmologic monitoring are offered, prescribers should be
331 aware of the possibility of long-term ophthalmologic effects (see CLINICAL
332 PHARMACOLOGY: Melanin Binding).

333 **Corneal Opacities:** Sumatriptan causes corneal opacities and defects in the corneal epithelium
334 in dogs; this raises the possibility that these changes may occur in humans. While patients were
335 not systematically evaluated for these changes in clinical trials, and no specific recommendations
336 for monitoring are being offered, prescribers should be aware of the possibility of these changes
337 (see CLINICAL PHARMACOLOGY: Corneal Opacities).

338 **Patients who are advised to self-administer IMITREX Injection in medically**
339 **unsupervised situations should receive instruction on the proper use of the product from**

340 **the physician or other suitably qualified health care professional prior to doing so for the**
341 **first time.**

342 **Information for Patients:** With the autoinjector, the needle penetrates approximately 1/4 of an
343 inch (5 to 6 mm). Since the injection is intended to be given subcutaneously, intramuscular or
344 intravascular delivery should be avoided. Patients should be directed to use injection sites with an
345 adequate skin and subcutaneous thickness to accommodate the length of the needle. See
346 PATIENT INFORMATION at the end of this labeling for the text of the separate leaflet provided
347 for patients.

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

350 **Drug Interactions:** There is no evidence that concomitant use of migraine prophylactic
351 medications has any effect on the efficacy of sumatriptan. In 2 Phase III trials in the US, a
352 retrospective analysis of 282 patients who had been using prophylactic drugs (verapamil n = 63,
353 amitriptyline n = 57, propranolol n = 94, for 45 other drugs n = 123) were compared to those who
354 had not used prophylaxis (N = 452). There were no differences in relief rates at 60 minutes
355 postdose for IMITREX Injection, whether or not prophylactic medications were used.

356 Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because
357 there is a theoretical basis that these effects may be additive, use of ergotamine-containing or
358 ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan within
359 24 hours of each other should be avoided (see CONTRAINDICATIONS).

360 MAO-A inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure.
361 Therefore, the use of sumatriptan in patients receiving MAO-A inhibitors is not ordinarily
362 recommended. If the clinical situation warrants the combined use of sumatriptan and an MAOI,
363 the dose of sumatriptan employed should be reduced (see CLINICAL PHARMACOLOGY: Drug
364 Interactions: *Monoamine Oxidase Inhibitors* and WARNINGS: Concomitant Drug Use).

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

369 **Drug/Laboratory Test Interactions:** IMITREX is not known to interfere with commonly
370 employed clinical laboratory tests.

371 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In carcinogenicity studies, rats
372 and mice were given sumatriptan by oral gavage (rats, 104 weeks) or drinking water (mice,
373 78 weeks). Average exposures achieved in mice receiving the highest dose were approximately
374 110 times the exposure attained in humans after the maximum recommended single dose of
375 6 mg. The highest dose to rats was approximately 260 times the maximum single dose of 6 mg on
376 a mg/m² basis. There was no evidence of an increase in tumors in either species related to
377 sumatriptan administration.

378 Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested
379 in 2 gene mutation assays (the Ames test and the in vitro mammalian Chinese hamster
380 V79/HGPRT assay). In 2 cytogenetics assays (the in vitro human lymphocyte assay and the in
381 vivo rat micronucleus assay) sumatriptan was not associated with clastogenic activity.

382 A fertility study (Segment I) by the subcutaneous route, during which male and female rats
383 were dosed daily with sumatriptan prior to and throughout the mating period, has shown no
384 evidence of impaired fertility at doses equivalent to approximately 100 times the maximum
385 recommended single human dose of 6 mg on a mg/m^2 basis. However, following oral
386 administration, a treatment-related decrease in fertility, secondary to a decrease in mating, was
387 seen for rats treated with 50 and 500 $\text{mg}/\text{kg}/\text{day}$. The no-effect dose for this finding was
388 approximately 8 times the maximum recommended single human dose of 6 mg on a mg/m^2 basis.

389 It is not clear whether the problem is associated with the treatment of males or females or both.
390 **Pregnancy:** Pregnancy Category C. Sumatriptan has been shown to be embryolethal in rabbits
391 when given daily at a dose approximately equivalent to the maximum recommended single
392 human subcutaneous dose of 6 mg on a mg/m^2 basis. There is no evidence that establishes that
393 sumatriptan is a human teratogen; however, there are no adequate and well-controlled studies in
394 pregnant women. IMITREX Injection should be used during pregnancy only if the potential
395 benefit justifies the potential risk to the fetus.

396 In assessing this information, the following additional findings should be considered.

397 **Embryolethality:** When given intravenously to pregnant rabbits daily throughout the period
398 of organogenesis, sumatriptan caused embryolethality at doses at or close to those producing
399 maternal toxicity. The mechanism of the embryolethality is not known. These doses were
400 approximately equivalent to the maximum single human dose of 6 mg on a mg/m^2 basis.

401 The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at
402 doses that are approximately 20 times a human dose of 6 mg on a mg/m^2 basis, did not cause
403 embryolethality. Additionally, in a study of pregnant rats given subcutaneous sumatriptan daily
404 prior to and throughout pregnancy, there was no evidence of increased embryo/fetal lethality.

405 **Teratogenicity:** Term fetuses from Dutch Stride rabbits treated during organogenesis with
406 oral sumatriptan exhibited an increased incidence of cervicothoracic vascular and skeletal
407 abnormalities. The functional significance of these abnormalities is not known. The highest
408 no-effect dose for these effects was 15 $\text{mg}/\text{kg}/\text{day}$, approximately 50 times the maximum single
409 dose of 6 mg on a mg/m^2 basis.

410 In a study in rats dosed daily with subcutaneous sumatriptan prior to and throughout
411 pregnancy, there was no evidence of teratogenicity.

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

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

417 **Pediatric Use:** Safety and effectiveness of IMITREX Injection in pediatric patients under 18
418 years of age have not been established; therefore, IMITREX Injection is not recommended for
419 use in patients under 18 years of age.

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

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

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

440 **Geriatric Use:** The use of sumatriptan in elderly patients is not recommended because elderly
441 patients are more likely to have decreased hepatic function, they are at higher risk for CAD, and
442 blood pressure increases may be more pronounced in the elderly (see WARNINGS: Risk of
443 Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events).

444 **ADVERSE REACTIONS**

445 **Serious cardiac events, including some that have been fatal, have occurred following the**
446 **use of IMITREX Injection or Tablets. These events are extremely rare and most have been**
447 **reported in patients with risk factors predictive of CAD. Events reported have included**
448 **coronary artery vasospasm, transient myocardial ischemia, myocardial infarction,**
449 **ventricular tachycardia, and ventricular fibrillation** (see CONTRAINDICATIONS,
450 WARNINGS: Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events,
451 and PRECAUTIONS: General).

452 Significant hypertensive episodes, including hypertensive crises, have been reported on rare
 453 occasions in patients with or without a history of hypertension (see WARNINGS: Increase in
 454 Blood Pressure).

455 Among patients in clinical trials of subcutaneous IMITREX Injection (N = 6,218), up to 3.5%
 456 of patients withdrew for reasons related to adverse events.

457 **Incidence in Controlled Clinical Trials of Migraine Headache:** Table 4 lists adverse
 458 events that occurred in 2 large US, Phase III, placebo-controlled clinical trials in migraine
 459 patients following either a single 6-mg dose of IMITREX Injection or placebo. Only events that
 460 occurred at a frequency of 2% or more in groups treated with IMITREX Injection 6 mg and
 461 occurred at a frequency greater than the placebo group are included in Table 4.

462

463 **Table 4. Treatment-Emergent Adverse Experience Incidence in 2 Large**
 464 **Placebo-Controlled Migraine Clinical Trials: Events Reported by at Least 2% of**
 465 **Patients Treated With IMITREX Injection 6 mg***

Adverse Event	Percent of Patients Reporting	
	IMITREX Injection 6 mg Subcutaneous (n = 547)	Placebo (n = 370)
Atypical sensations	42	9
Tingling	14	3
Warm/hot sensation	11	4
Burning sensation	7	<1
Feeling of heaviness	7	1
Pressure sensation	7	2
Feeling of tightness	5	<1
Numbness	5	2
Feeling strange	2	<1
Tight feeling in head	2	<1
Cardiovascular		
Flushing	7	2
Chest discomfort	5	1
Tightness in chest	3	<1
Pressure in chest	2	<1
Ear, nose, and throat		
Throat discomfort	3	<1
Discomfort: nasal cavity/sinuses	2	<1
Injection site reaction	59	24
Miscellaneous		

Jaw discomfort	2	0
Musculoskeletal		
Weakness	5	<1
Neck pain/stiffness	5	<1
Myalgia	2	<1
Neurological		
Dizziness/vertigo	12	4
Drowsiness/sedation	3	2
Headache	2	<1
Skin		
Sweating	2	1

*The sum of the percentages cited is greater than 100% because patients may experience more than 1 type of adverse event. Only events that occurred at a frequency of 2% or more in groups treated with IMITREX Injection and occurred at a frequency greater than the placebo groups are included.

466

467 The incidence of adverse events in controlled clinical trials was not affected by gender or age
468 of the patients. There were insufficient data to assess the impact of race on the incidence of
469 adverse events.

470 **Incidence in Controlled Trials of Cluster Headache:** In the controlled clinical trials
471 assessing sumatriptan's efficacy as a treatment for cluster headache, no new significant adverse
472 events associated with the use of sumatriptan were detected that had not already been identified
473 in association with the drug's use in migraine.

474 Overall, the frequency of adverse events reported in the studies of cluster headache were
475 generally lower. Exceptions include reports of paresthesia (5% IMITREX, 0% placebo), nausea
476 and vomiting (4% IMITREX, 0% placebo), and bronchospasm (1% IMITREX, 0% placebo).

477 **Other Events Observed in Association With the Administration of IMITREX**
478 **Injection:** In the paragraphs that follow, the frequencies of less commonly reported adverse
479 clinical events are presented. Because the reports include events observed in open and
480 uncontrolled studies, the role of IMITREX Injection in their causation cannot be reliably
481 determined. Furthermore, variability associated with adverse event reporting, the terminology
482 used to describe adverse events, etc., limit the value of the quantitative frequency estimates
483 provided.

484 Event frequencies are calculated as the number of patients reporting an event divided by the
485 total number of patients (N = 6,218) exposed to subcutaneous IMITREX Injection. All reported
486 events are included except those already listed in the previous table, those too general to be
487 informative, and those not reasonably associated with the use of the drug. Events are further

488 classified within body system categories and enumerated in order of decreasing frequency using
489 the following definitions: frequent adverse events are defined as those occurring in at least 1/100
490 patients, infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, and rare
491 adverse events are those occurring in fewer than 1/1,000 patients.

492 **Cardiovascular:** Infrequent were hypertension, hypotension, bradycardia, tachycardia,
493 palpitations, pulsating sensations, various transient ECG changes (nonspecific ST or T wave
494 changes, prolongation of PR or QTc intervals, sinus arrhythmia, nonsustained ventricular
495 premature beats, isolated junctional ectopic beats, atrial ectopic beats, delayed activation of the
496 right ventricle), and syncope. Rare were pallor, arrhythmia, abnormal pulse, vasodilatation, and
497 Raynaud syndrome.

498 **Endocrine and Metabolic:** Infrequent was thirst. Rare were polydipsia and dehydration.

499 **Eye:** Frequent was vision alterations. Infrequent was irritation of the eye.

500 **Gastrointestinal:** Frequent were abdominal discomfort and dysphagia. Infrequent were
501 gastroesophageal reflux and diarrhea. Rare were peptic ulcer, retching, flatulence/eructation, and
502 gallstones.

503 **Musculoskeletal:** Frequent were muscle cramps. Infrequent were various joint disturbances
504 (pain, stiffness, swelling, ache). Rare were muscle stiffness, need to flex calf muscles, backache,
505 muscle tiredness, and swelling of the extremities.

506 **Neurological:** Frequent was anxiety. Infrequent were mental confusion, euphoria, agitation,
507 relaxation, chills, sensation of lightness, tremor, shivering, disturbances of taste, prickling
508 sensations, paresthesia, stinging sensations, facial pain, photophobia, and lacrimation. Rare were
509 transient hemiplegia, hysteria, globus hystericus, intoxication, depression, myoclonia,
510 monoplegia/diplegia, sleep disturbance, difficulties in concentration, disturbances of smell,
511 hyperesthesia, dysesthesia, simultaneous hot and cold sensations, tickling sensations, dysarthria,
512 yawning, reduced appetite, hunger, and dystonia.

513 **Respiratory:** Infrequent was dyspnea. Rare were influenza, diseases of the lower respiratory
514 tract, and hiccoughs.

515 **Skin:** Infrequent were erythema, pruritus, and skin rashes and eruptions. Rare was skin
516 tenderness.

517 **Urogenital:** Rare were dysuria, frequency, dysmenorrhea, and renal calculus.

518 **Miscellaneous:** Infrequent were miscellaneous laboratory abnormalities, including minor
519 disturbances in liver function tests, "serotonin agonist effect," and hypersensitivity to various
520 agents. Rare was fever.

521 **Other Events Observed in the Clinical Development of IMITREX:** The following
522 adverse events occurred in clinical trials with IMITREX Tablets and IMITREX Nasal Spray.
523 Because the reports include events observed in open and uncontrolled studies, the role of
524 IMITREX in their causation cannot be reliably determined. All reported events are included

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

527 **Breasts:** Breast swelling, cysts, disorder of breasts, lumps, masses of breasts, nipple
528 discharge, primary malignant breast neoplasm, and tenderness.

529 **Cardiovascular:** Abdominal aortic aneurysm, angina, atherosclerosis, cerebral ischemia,
530 cerebrovascular lesion, heart block, peripheral cyanosis, phlebitis, thrombosis, and transient
531 myocardial ischemia.

532 **Ear, Nose, and Throat:** Allergic rhinitis; disorder of nasal cavity/sinuses; ear, nose, and
533 throat hemorrhage; ear infection; external otitis; feeling of fullness in the ear(s); hearing
534 disturbances; hearing loss; Meniere disease; nasal inflammation; otalgia; sensitivity to noise;
535 sinusitis; tinnitus; and upper respiratory inflammation.

536 **Endocrine and Metabolic:** Elevated thyrotropin stimulating hormone (TSH) levels;
537 endocrine cysts, lumps, and masses; fluid disturbances; galactorrhea; hyperglycemia;
538 hypoglycemia; hypothyroidism; weight gain; and weight loss.

539 **Eye:** Accommodation disorders, blindness and low vision, conjunctivitis, disorders of sclera,
540 external ocular muscle disorders, eye edema and swelling, eye hemorrhage, eye itching, eye pain,
541 keratitis, mydriasis, and visual disturbances.

542 **Gastrointestinal:** Abdominal distention, colitis, constipation, dental pain, dyspeptic
543 symptoms, feelings of gastrointestinal pressure, gastric symptoms, gastritis, gastroenteritis,
544 gastrointestinal bleeding, gastrointestinal pain, hematemesis, hypersalivation, hyposalivation,
545 intestinal obstruction, melena, nausea and/or vomiting, oral itching and irritation, pancreatitis,
546 salivary gland swelling, and swallowing disorders.

547 **Hematological Disorders:** Anemia.

548 **Mouth and Teeth:** Disorder of mouth and tongue (e.g., burning of tongue, numbness of
549 tongue, dry mouth).

550 **Musculoskeletal:** Acquired musculoskeletal deformity, arthralgia and articular rheumatitis,
551 arthritis, intervertebral disc disorder, muscle atrophy, muscle tightness and rigidity,
552 musculoskeletal inflammation, and tetany.

553 **Neurological:** Apathy, aggressiveness, bad/unusual taste, bradylogia, cluster headache,
554 convulsions, depressive disorders, detachment, disturbance of emotions, drug abuse, facial
555 paralysis, hallucinations, heat sensitivity, incoordination, increased alertness, memory
556 disturbance, migraine, motor dysfunction, neoplasm of pituitary, neuralgia, neurotic disorders,
557 paralysis, personality change, phobia, phonophobia, psychomotor disorders, radiculopathy,
558 raised intracranial pressure, rigidity, stress, syncope, suicide, and twitching.

559 **Respiratory:** Asthma, breathing disorders, bronchitis, cough, and lower respiratory tract
560 infection.

561 **Skin:** Dry/scaly skin, eczema, herpes, seborrheic dermatitis, skin nodules, tightness of skin,
562 and wrinkling of skin.

563 **Urogenital:** Abnormal menstrual cycle, abortion, bladder inflammation, endometriosis,
564 hematuria, increased urination, inflammation of fallopian tubes, intermenstrual bleeding,
565 menstruation symptoms, micturition disorders, urethritis, and urinary infections.

566 **Miscellaneous:** Contusions, difficulty in walking, edema, hematoma, hypersensitivity,
567 fever, fluid retention, lymphadenopathy, overdose, speech disturbance, swelling of extremities,
568 swelling of face, and voice disturbances.

569 **Pain and Other Pressure Sensations:** Chest pain and/or heaviness, neck/throat/jaw
570 pain/tightness/pressure, and pain (location specified).

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

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

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

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

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

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

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

589 **Neurological:** Central nervous system vasculitis, cerebrovascular accident, dysphasia,
590 subarachnoid hemorrhage.

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

593 **Psychiatry:** Panic disorder.

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

595 **Skin:** Exacerbation of sunburn, hypersensitivity reactions (allergic vasculitis, erythema,
596 pruritus, rash, shortness of breath, urticaria; in addition, severe anaphylaxis/anaphylactoid
597 reactions have been reported [see WARNINGS: Hypersensitivity]), photosensitivity. Following
598 subcutaneous administration of sumatriptan, pain, redness, stinging, induration, swelling,
599 contusion, subcutaneous bleeding, and, on rare occasions, lipoatrophy (depression in the skin) or
600 lipohypertrophy (enlargement or thickening of tissue) have been reported.

601 **Urogenital:** Acute renal failure.

602 **DRUG ABUSE AND DEPENDENCE**

603 The abuse potential of IMITREX Injection cannot be fully delineated in advance of extensive
604 marketing experience. One clinical study enrolling 12 patients with a history of substance abuse
605 failed to induce subjective behavior and/or physiologic response ordinarily associated with drugs
606 that have an established potential for abuse.

607 **OVERDOSAGE**

608 Patients (N = 269) have received single injections of 8 to 12 mg without significant adverse
609 effects. Volunteers (N = 47) have received single subcutaneous doses of up to 16 mg without
610 serious adverse events.

611 No gross overdoses in clinical practice have been reported. Coronary vasospasm was observed
612 after intravenous administration of IMITREX Injection (see CONTRAINDICATIONS).
613 Overdoses would be expected from animal data (dogs at 0.1 g/kg, rats at 2 g/kg) to possibly cause
614 convulsions, tremor, inactivity, erythema of the extremities, reduced respiratory rate, cyanosis,
615 ataxia, mydriasis, injection site reactions (desquamation, hair loss, and scab formation), and
616 paralysis. The half-life of elimination of sumatriptan is about 2 hours (see CLINICAL
617 PHARMACOLOGY: Pharmacokinetics), and therefore monitoring of patients after overdose
618 with IMITREX Injection should continue while symptoms or signs persist, and for at least
619 10 hours.

620 It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations
621 of sumatriptan.

622 **DOSAGE AND ADMINISTRATION**

623 The maximum single recommended adult dose of IMITREX Injection is 6 mg injected
624 subcutaneously. If side effects are dose limiting, then lower doses may be used (see Table 1).

625 The maximum recommended dose that may be given in 24 hours is two 6-mg injections
626 separated by at least 1 hour. Controlled clinical trials have failed to show that clear benefit is
627 associated with the administration of a second 6-mg dose in patients who have failed to respond
628 to a first injection.

629 In patients receiving MAO inhibitors, decreased doses of sumatriptan should be considered
630 (see WARNINGS: Concomitant Drug Use and CLINICAL PHARMACOLOGY: Drug
631 Interactions: *Monoamine Oxidase Inhibitors*).

632 An autoinjection device is available for use with the 4- and 6-mg prefilled syringe cartridges
633 to facilitate self-administration in patients using the 4- or 6-mg dose. With this device, the needle
634 penetrates approximately 1/4 inch (5 to 6 mm). Since the injection is intended to be given
635 subcutaneously, intramuscular or intravascular delivery should be avoided. Patients should be

636 directed to use injection sites with an adequate skin and subcutaneous thickness to accommodate
637 the length of the needle.

638 In patients receiving doses other than 4 or 6 mg, only the 6-mg single-dose vial dosage form
639 should be used. Parenteral drug products should be inspected visually for particulate matter and
640 discoloration before administration whenever solution and container permit.

641 **HOW SUPPLIED**

642 IMITREX Injection contains sumatriptan (base) as the succinate salt and is supplied as a clear,
643 colorless to pale yellow, sterile, nonpyrogenic solution as follows:

644 (NDC 0173-0739-00) IMITREX STATdose System[®], 4 mg, containing 2 prefilled single-dose
645 syringe cartridges, 1 IMITREX STATdose Pen[®], and instructions for use.

646 (NDC 0173-0739-02) Two 4-mg single-dose prefilled syringe cartridges for use with IMITREX
647 STATdose System.

648 (NDC 0173-0479-00) IMITREX STATdose System, 6 mg, containing 2 prefilled single-dose
649 syringe cartridges, 1 IMITREX STATdose Pen, and instructions for use.

650 (NDC 0173-0478-00) Two 6-mg single-dose prefilled syringe cartridges for use with IMITREX
651 STATdose System.

652 (NDC 0173-0449-02) IMITREX Injection single-dose vial (6 mg/0.5 mL) in cartons containing 5
653 vials.

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

655 **PATIENT INFORMATION**

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

657

658

Information for the Patient

659

IMITREX[®] (sumatriptan succinate) Injection

660

661 Please read this leaflet carefully before you take IMITREX Injection. This leaflet provides a
662 summary of the information available about your medicine. Please do not throw away this leaflet
663 until you have finished your medicine. You may need to read this leaflet again. This leaflet does
664 not contain all the information on IMITREX Injection. For further information or advice, ask
665 your doctor or pharmacist.

Information About Your Medicine:

666 The name of your medicine is IMITREX (sumatriptan succinate) Injection. It can be obtained
667 only by prescription from your doctor. The decision to use IMITREX Injection is one that you
668 and your doctor should make jointly, taking into account your individual preferences and
669 medical circumstances. If you have risk factors for heart disease (such as high blood pressure,
670 high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are
671 postmenopausal or a male over 40), you should tell your doctor, who should evaluate you for
672

673 heart disease in order to determine if IMITREX is appropriate for you. Although the vast
674 majority of those who have taken IMITREX have not experienced any significant side effects,
675 some individuals have experienced serious heart problems and, rarely, considering the extensive
676 use of IMITREX worldwide, deaths have been reported. In all but a few instances, however,
677 serious problems occurred in people with known heart diseases and it was not clear whether
678 IMITREX was a contributory factor in these deaths.

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

680 IMITREX Injection is intended to relieve your migraine or cluster headache, but not to
681 prevent or reduce the number of attacks you experience. Use IMITREX Injection only to treat an
682 actual migraine or cluster headache attack.

683 ***2. Important Questions to Consider Before Taking IMITREX Injection:***

684 If the answer to any of the following questions is **YES** or if you do not know the answer, then
685 please discuss with your doctor before you use IMITREX Injection.

- 686 • Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant?
687 Are you using inadequate contraception? Are you breastfeeding?
- 688 • Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have
689 you had a heart attack?
- 690 • Do you have risk factors for heart disease (such as high blood pressure, high cholesterol,
691 obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal
692 or a male over 40)?
- 693 • Have you had a stroke, transient ischemic attacks (TIAs), or Raynaud syndrome?
- 694 • Do you have high blood pressure?
- 695 • Have you ever had to stop taking this or any other medicine because of an allergy or other
696 problems?
- 697 • Are you taking any other migraine medicines, including other 5-HT₁ agonists or any other
698 medicines containing ergotamine, dihydroergotamine, or methysergide?
- 699 • Are you taking any medicine for depression (monoamine oxidase inhibitors or selective
700 serotonin reuptake inhibitors [SSRIs])?
- 701 • Have you had, or do you have, any disease of the liver or kidney?
- 702 • Have you had, or do you have, epilepsy or seizures?
- 703 • Is this headache different from your usual migraine attacks?

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

706 ***3. The Use of IMITREX Injection During Pregnancy:***

707 Do not use IMITREX Injection if you are pregnant, think you might be pregnant, are trying to
708 become pregnant, or are not using adequate contraception, unless you have discussed this with
709 your doctor.

710 ***4. How to Use IMITREX Injection:***

711 Before injecting IMITREX, check with your doctor on acceptable injection sites and see the
712 instructions inside the carton on discarding empty syringes and reloading an autoinjector device.

713 **Never reuse a syringe.**

714 For adults, the usual dose is a single injection given just below the skin. It should be given as
715 soon as the symptoms of your migraine appear, but it may be given at any time during an attack.
716 A second injection may be given if your symptoms of migraine come back. If your symptoms do
717 not improve following the first injection, do not give a second injection for the same attack
718 without first consulting with your doctor. Do not administer more than two 6-mg doses in any
719 24 hours and allow at least 1 hour between each dose.

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

- 721 • Some patients experience pain or tightness in the chest or throat when using IMITREX
722 Injection. If this happens to you, then discuss it with your doctor before using any more
723 IMITREX Injection. If the chest pain is severe or does not go away, call your doctor
724 immediately.
- 725 • If you have sudden and/or severe abdominal pain following IMITREX Injection, call your
726 doctor immediately.
- 727 • Shortness of breath; wheeziness; heart throbbing; swelling of eyelids, face, or lips; or a skin
728 rash, skin lumps, or hives happens rarely. If it happens to you, then tell your doctor
729 immediately. Do not take any more IMITREX Injection unless your doctor tells you to do so.
- 730 • Some people may have feelings of tingling, heat, flushing (redness of face lasting a short
731 time), heaviness or pressure after treatment with IMITREX Injection. A few people may feel
732 drowsy, dizzy, tired, or sick. Tell your doctor of these symptoms at your next visit.
- 733 • You may experience pain or redness at the site of injection, but this usually lasts less than an
734 hour.
- 735 • If you feel unwell in any other way or have any symptoms that you do not understand, you
736 should contact your doctor immediately.

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

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

740 **7. Storing Your Medicine:**

741 Keep your medicine in a safe place where children cannot reach it. It may be harmful to
742 children.

743 Store your medicine away from heat and light. Keep your medicine in the case provided and
744 do not store at temperatures above 86°F (30°C).

745 If your medicine has expired (the expiration date is printed on the treatment pack), throw it
746 away as instructed. Do not throw away your autoinjector.

747 If your doctor decides to stop your treatment, do not keep any leftover medicine unless your
748 doctor tells you to. Throw away your medicine as instructed.

NDA 20-080/S-036

Package Insert

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749

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GlaxoSmithKline

751

752 GlaxoSmithKline

753 Research Triangle Park, NC 27709

754

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757 January 2006

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/s/

Russell Katz

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