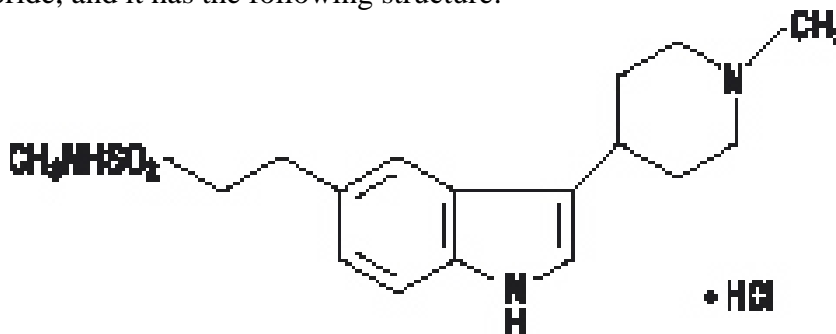


## PRESCRIBING INFORMATION

# AMERGE<sup>®</sup> (natriptan hydrochloride) Tablets

### DESCRIPTION

AMERGE Tablets contain natriptan as the hydrochloride, which is a selective 5-hydroxytryptamine<sub>1</sub> receptor subtype agonist. Natriptan hydrochloride is chemically designated as N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide monohydrochloride, and it has the following structure:



The empirical formula is  $C_{17}H_{25}N_3O_2S \cdot HCl$ , representing a molecular weight of 371.93. Natriptan hydrochloride is a white to pale yellow powder that is readily soluble in water. Each AMERGE Tablet for oral administration contains 1.11 or 2.78 mg of natriptan hydrochloride equivalent to 1 or 2.5 mg of natriptan, respectively. Each tablet also contains the inactive ingredients croscarmellose sodium; hypromellose; lactose; magnesium stearate; microcrystalline cellulose; triacetin; and titanium dioxide, iron oxide yellow (2.5-mg tablet only), and indigo carmine aluminum lake (FD&C Blue No. 2) (2.5-mg tablet only) for coloring.

### CLINICAL PHARMACOLOGY

**Mechanism of Action:** Natriptan binds with high affinity to 5-HT<sub>1D</sub> and 5-HT<sub>1B</sub> receptors and has no significant affinity or pharmacological activity at 5-HT<sub>2-4</sub> receptor subtypes or at adrenergic  $\alpha_1$ ,  $\alpha_2$ , or  $\beta$ ; dopaminergic D<sub>1</sub> or D<sub>2</sub>; muscarinic; or benzodiazepine receptors.

The therapeutic activity of natriptan in migraine is generally attributed to its agonist activity at 5-HT<sub>1D/1B</sub> receptors. Two current theories have been proposed to explain the efficacy of 5-HT<sub>1D/1B</sub> receptor agonists in migraine. One theory suggests that activation of 5-HT<sub>1D/1B</sub> receptors located on intracranial blood vessels, including those on the arteriovenous anastomoses, leads to vasoconstriction, which is correlated with the relief of migraine headache. The other hypothesis suggests that activation of 5-HT<sub>1D/1B</sub> receptors on sensory nerve endings in the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release.

In the anesthetized dog, natriptan has been shown to reduce the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. While the effect on blood flow was selective for the carotid arterial bed, increases in vascular resistance of up to 30% were seen in the coronary arterial bed. Natriptan has also been shown to inhibit trigeminal

33 nerve activity in rat and cat. In 10 human subjects with suspected coronary artery disease (CAD)  
34 undergoing coronary artery catheterization, there was a 1% to 10% reduction in coronary artery  
35 diameter following subcutaneous injection of 1.5 mg of naratriptan.

36 **Pharmacokinetics:** Naratriptan tablets are well absorbed, with about 70% oral bioavailability.  
37 Following administration of a 2.5-mg tablet orally, the peak concentrations are obtained in 2 to  
38 3 hours. After administration of 1- or 2.5-mg tablets, the  $C_{max}$  is somewhat (about 50%) higher in  
39 women (not corrected for milligram-per-kilogram dose) than in men. During a migraine attack,  
40 absorption was slower, with a  $T_{max}$  of 3 to 4 hours. Food does not affect the pharmacokinetics of  
41 naratriptan. Naratriptan displays linear kinetics over the therapeutic dose range.

42 The steady-state volume of distribution of naratriptan is 170 L. Plasma protein binding is 28%  
43 to 31% over the concentration range of 50 to 1,000 ng/mL.

44 Naratriptan is predominantly eliminated in urine, with 50% of the dose recovered unchanged  
45 and 30% as metabolites in urine. In vitro, naratriptan is metabolized by a wide range of  
46 cytochrome P450 isoenzymes into a number of inactive metabolites.

47 The mean elimination half-life of naratriptan is 6 hours. The systemic clearance of naratriptan  
48 is 6.6 mL/min/kg. The renal clearance (220 mL/min) exceeds glomerular filtration rate,  
49 indicating active tubular secretion. Repeat administration of naratriptan tablets does not result in  
50 drug accumulation.

51 **Special Populations: Age:** A small decrease in clearance (approximately 26%) was observed  
52 in healthy elderly subjects (65 to 77 years) compared to younger patients, resulting in slightly  
53 higher exposure (see PRECAUTIONS).

54 **Race:** The effect of race on the pharmacokinetics of naratriptan has not been examined.

55 **Renal Impairment:** Clearance of naratriptan was reduced by 50% in patients with moderate  
56 renal impairment (creatinine clearance: 18 to 39 mL/min) compared to the normal group.  
57 Decrease in clearances resulted in an increase of mean half-life from 6 hours (healthy) to  
58 11 hours (range: 7 to 20 hours). The mean  $C_{max}$  increased by approximately 40%. The effects of  
59 severe renal impairment (creatinine clearance:  $\leq 15$  mL/min) on the pharmacokinetics of  
60 naratriptan has not been assessed (see CONTRAINDICATIONS and DOSAGE AND  
61 ADMINISTRATION).

62 **Hepatic Impairment:** Clearance of naratriptan was decreased by 30% in patients with  
63 moderate hepatic impairment (Child-Pugh grade A or B). This resulted in an approximately 40%  
64 increase in the half-life (range: 8 to 16 hours). The effects of severe hepatic impairment (Child-  
65 Pugh grade C) on the pharmacokinetics of naratriptan have not been assessed (see  
66 CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

67 **Drug Interactions:** In normal volunteers, coadministration of single doses of naratriptan  
68 tablets and alcohol did not result in substantial modification of naratriptan pharmacokinetic  
69 parameters.

70 From population pharmacokinetic analyses, coadministration of naratriptan and fluoxetine,  
71 beta-blockers, or tricyclic antidepressants did not affect the clearance of naratriptan.

72 Naratriptan does not inhibit monoamine oxidase (MAO) enzymes and is a poor inhibitor of  
73 P450; metabolic interactions between naratriptan and drugs metabolized by P450 or MAO are  
74 therefore unlikely.

75 **Oral Contraceptives:** Oral contraceptives reduced clearance by 32% and volume of  
76 distribution by 22%, resulting in slightly higher concentrations of naratriptan. Hormone  
77 replacement therapy had no effect on pharmacokinetics in older female patients.

78 Smoking increased the clearance of naratriptan by 30%.

## 79 CLINICAL TRIALS

80 The efficacy of AMERGE Tablets in the acute treatment of migraine headaches was evaluated  
81 in 6 randomized, double-blind, placebo-controlled studies of which 4 used the recommended  
82 dosing regimen and were conducted as outpatient trials. Three of these studies enrolled adult  
83 patients who were predominantly female (86%) and Caucasian (96%) with a mean age of 41  
84 (range: 18 to 65). One study enrolled adolescents with a mean age of 14 (range: 12 to 17). In the  
85 adolescent study, 54% of the patients were female and 89% were Caucasian. In all studies,  
86 patients were instructed to treat at least 1 moderate to severe headache. Headache response,  
87 defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was  
88 assessed up to 4 hours after dosing. Associated symptoms such as nausea, vomiting,  
89 photophobia, and phonophobia were also assessed. Maintenance of response was assessed for up  
90 to 24 hours postdose. A second dose of AMERGE Tablets or other medication was allowed 4 to  
91 24 hours after the initial treatment for recurrent headache. The frequency and time to use of these  
92 additional treatments were also determined.

93 In all 3 trials in adults utilizing the recommended dosage regimen and outpatient use, the  
94 percentage of patients achieving headache response 4 hours after treatment, the primary outcome  
95 measure, was significantly greater among patients receiving AMERGE compared to those who  
96 received placebo. In all studies, response to 2.5 mg was numerically greater than response to  
97 1 mg and in the largest of the 3 studies, there was a statistically significant greater percentage of  
98 patients with headache response at 4 hours in the 2.5-mg group compared to the 1-mg group. The  
99 results are summarized in Table 1.

100

101 **Table 1. Percentage of Adult Patients With Headache Response (Mild or No Headache)**  
102 **4 Hours Following Treatment**

	Placebo	AMERGE 1.0 mg	AMERGE 2.5 mg
Study 1	34% (n = 122)	50% <sup>a</sup> (n = 117)	60% <sup>a</sup> (n = 127)
Study 2	27% (n = 104)	52% <sup>a</sup> (n = 208)	66% <sup>ab</sup> (n = 199)
Study 3	32% (n = 169)	54% <sup>a</sup> (n = 166)	65% <sup>a</sup> (n = 167)

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

104 <sup>b</sup>p<0.05 in comparison with 1 mg.

105

106 In the single study in adolescents, there were no statistically significant differences between  
107 any of the treatment groups. The headache response rates at 4 hours (n) were 65% (n = 74), 67%  
108 (n = 78), and 64% (n = 70) for placebo, 1-mg, and 2.5-mg groups, respectively.

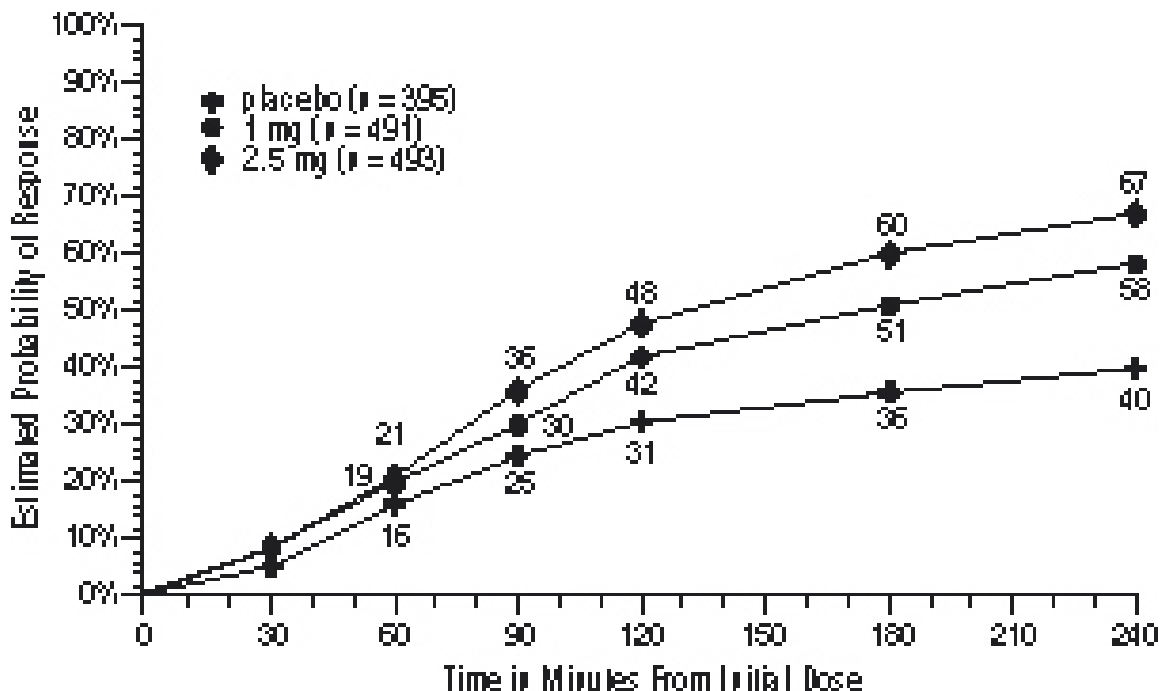
109 **Comparisons of drug performance based upon results obtained in different clinical trials**  
110 **are never reliable. Because studies are conducted at different times, with different samples**  
111 **of patients, by different investigators, employing different criteria and/or different**  
112 **interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.),**  
113 **quantitative estimates of treatment response and the timing of response may be expected to**  
114 **vary considerably from study to study.**

115 The estimated probability of achieving an initial headache response in adults over the 4 hours  
116 following treatment is depicted in Figure 1.

117

118 **Figure 1. Estimated Probability of Achieving Initial Headache Response Within**  
119 **4 Hours<sup>a</sup>**

120



121

122 <sup>a</sup> The figure shows the probability over time of obtaining headache response (no or mild  
123 pain) following treatment with AMERGE Tablets. The averages displayed are based  
124 on pooled data from the 3 controlled clinical trials providing evidence of efficacy  
125 (Studies 1, 2, and 3). In this Kaplan-Meier plot, patients not achieving response within  
126 240 minutes were censored at 240 minutes.

127

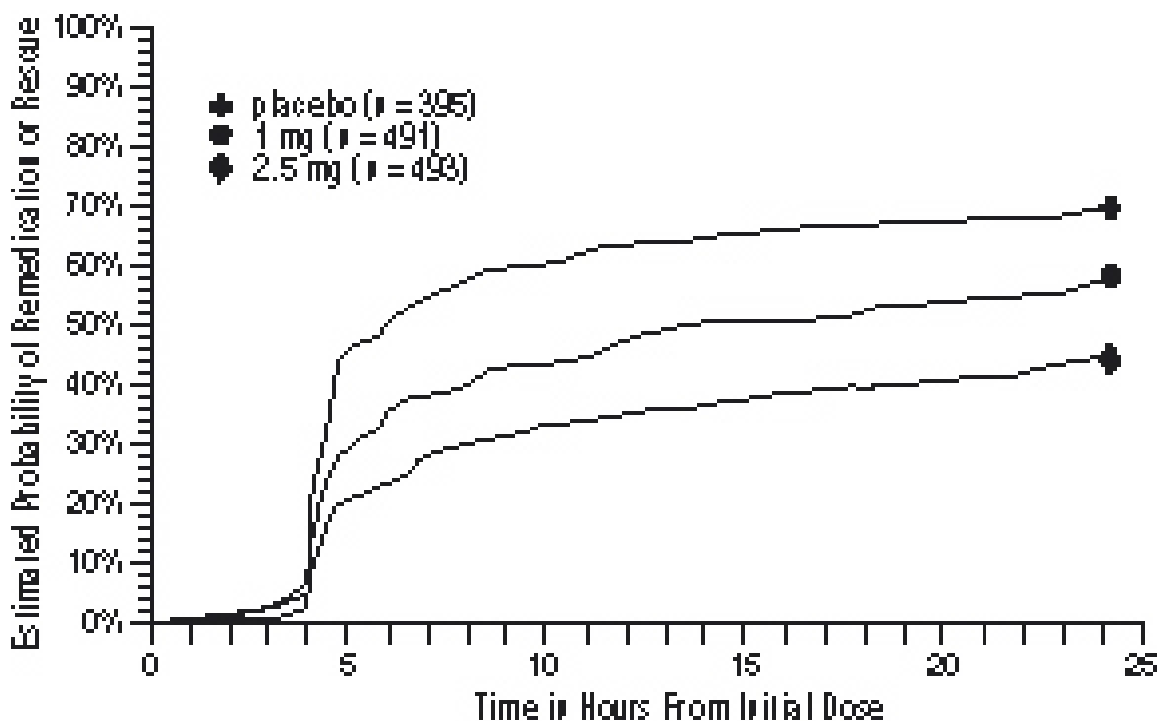
128 For patients with migraine-associated nausea, photophobia, and phonophobia at baseline,  
129 there was a lower incidence of these symptoms 4 hours following administration of 1- and 2.5-  
130 mg AMERGE Tablets compared to placebo.

131 Four to 24 hours following the initial dose of study treatment, patients were allowed to use  
132 additional treatment for pain relief in the form of a second dose of study treatment or other  
133 medication. The estimated probability of patients taking a second dose or other medication for  
134 migraine over the 24 hours following the initial dose of study treatment is summarized in  
135 Figure 2.

136

137 **Figure 2. Estimated Probability of Patients Taking a Second Dose of AMERGE**  
138 **Tablets or Other Medication for Migraine Over the 24 Hours Following the Initial**  
139 **Dose of Study Treatment<sup>a</sup>**

140



141

142 <sup>a</sup> Kaplan-Meier plot based on data obtained in the 3 controlled clinical trials (Studies 1,  
143 2, and 3) providing evidence of efficacy with patients not using additional treatments  
144 censored at 24 hours. The plot also includes patients who had no response to the initial  
145 dose. Remedication was discouraged prior to 4 hours postdose.

146

147 There is no evidence that doses of 5 mg provide a greater effect than 2.5 mg. There was no  
148 evidence to suggest that treatment with AMERGE was associated with an increase in the severity  
149 or frequency of migraine attacks. The efficacy of AMERGE Tablets was unaffected by presence  
150 of aura; gender, age, or weight of the patient; oral contraceptive use; or concomitant use of  
151 common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic  
152 antidepressants). There was insufficient data to assess the impact of race on efficacy.

153 **INDICATIONS AND USAGE**

154 AMERGE Tablets are indicated for the acute treatment of migraine attacks with or without  
155 aura in adults.

156 AMERGE Tablets are not intended for the prophylactic therapy of migraine or for use in the  
157 management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and  
158 effectiveness of AMERGE Tablets have not been established for cluster headache, which is  
159 present in an older, predominantly male population.

160 **CONTRAINDICATIONS**

161 AMERGE Tablets should not be given to patients with history, symptoms, or signs of  
162 ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients  
163 with other significant underlying cardiovascular diseases should not receive AMERGE  
164 Tablets. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any  
165 type (e.g., stable angina of effort, vasospastic forms of angina such as the Prinzmetal  
166 variant), all forms of myocardial infarction, and silent myocardial ischemia.  
167 Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as  
168 transient ischemic attacks. Peripheral vascular disease includes, but is not limited to,  
169 ischemic bowel disease (see WARNINGS).

170 Because AMERGE Tablets may increase blood pressure, they should not be given to  
171 patients with uncontrolled hypertension (see WARNINGS).

172 AMERGE Tablets are contraindicated in patients with severe renal impairment  
173 (creatinine clearance, <15 mL/min) (see CLINICAL PHARMACOLOGY and DOSAGE  
174 AND ADMINISTRATION).

175 AMERGE Tablets are contraindicated in patients with severe hepatic impairment  
176 (Child-Pugh grade C) (see CLINICAL PHARMACOLOGY and DOSAGE AND  
177 ADMINISTRATION).

178 AMERGE Tablets should not be administered to patients with hemiplegic or basilar  
179 migraine.

180 AMERGE Tablets should not be used within 24 hours of treatment with another 5-HT<sub>1</sub>  
181 agonist, an ergotamine-containing or ergot-type medication like dihydroergotamine or  
182 methysergide.

183 AMERGE Tablets are contraindicated in patients with hypersensitivity to naratriptan  
184 or any of the components.

185 **WARNINGS**

186 AMERGE Tablets should only be used where a clear diagnosis of migraine has been  
187 established.

188 **Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events:**  
189 **Because of the potential of this class of compounds (5-HT<sub>1B/1D</sub> agonists) to cause coronary**  
190 **vasospasm, naratriptan should not be given to patients with documented ischemic or**  
191 **vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly**

192 recommended that 5-HT<sub>1</sub> agonists (including naratriptan) not be given to patients in whom  
193 unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension,  
194 hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with  
195 surgical or physiological menopause, male over 40 years of age) unless a cardiovascular  
196 evaluation provides satisfactory clinical evidence that the patient is reasonably free of  
197 coronary artery and ischemic myocardial disease or other significant underlying  
198 cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect  
199 cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best.  
200 If, during the cardiovascular evaluation, the patient's medical history,  
201 electrocardiographic, or other investigations reveal findings indicative of, or consistent  
202 with, coronary artery vasospasm or myocardial ischemia, naratriptan should not be  
203 administered (see CONTRAINDICATIONS).

204 For patients with risk factors predictive of CAD, who are determined to have a  
205 satisfactory cardiovascular evaluation, it is strongly recommended that administration of  
206 the first dose of naratriptan take place in the setting of a physician's office or similar  
207 medically staffed and equipped facility. Because cardiac ischemia can occur in the absence  
208 of clinical symptoms, consideration should be given to obtaining on the first occasion of use  
209 an electrocardiogram (ECG) during the interval immediately following administration of  
210 AMERGE Tablets in these patients with risk factors.

211 It is recommended that patients who are intermittent long-term users of 5-HT<sub>1</sub> agonists,  
212 including AMERGE Tablets, and who have or acquire risk factors predictive of CAD, as  
213 described above, undergo periodic cardiovascular evaluation as they continue to use  
214 AMERGE Tablets.

215 The systematic approach described above is intended to reduce the likelihood that  
216 patients with unrecognized cardiovascular disease will be inadvertently exposed to  
217 naratriptan.

218 **Cardiac Events and Fatalities Associated With 5-HT<sub>1</sub> Agonists:** Naratriptan can cause  
219 coronary artery vasospasm (see CLINICAL PHARMACOLOGY). Serious adverse cardiac  
220 events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm,  
221 and death have been reported within a few hours following the administration of 5-HT<sub>1</sub> agonists.  
222 Considering the extent of use of 5-HT<sub>1</sub> agonists in patients with migraine, the incidence of these  
223 events is extremely low.

224 **Premarketing Experience With AMERGE Tablets:** Among approximately 3,500  
225 patients with migraine who participated in premarketing clinical trials of naratriptan tablets,  
226 4 patients treated with single oral doses of naratriptan ranging from 1 to 10 mg experienced  
227 asymptomatic ischemic ECG changes with at least 1, who took 7.5 mg, likely due to coronary  
228 vasospasm.

229 **Cerebrovascular Events and Fatalities With 5-HT<sub>1</sub> Agonists:** Cerebral hemorrhage,  
230 subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in  
231 patients treated with 5-HT<sub>1</sub> agonists, and some have resulted in fatalities. In a number of cases, it



232 appears possible that the cerebrovascular events were primary, the agonist having been  
233 administered in the incorrect belief that the symptoms experienced were a consequence of  
234 migraine, when they were not. It should be noted that patients with migraine may be at increased  
235 risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

236 **Other Vasospasm-Related Events:** 5-HT<sub>1</sub> agonists may cause vasospastic reactions other  
237 than coronary artery spasm. Both peripheral vascular ischemia and colonic ischemia with  
238 abdominal pain and bloody diarrhea have been reported with naratriptan.

239 **Serotonin Syndrome:** Serotonin syndrome may occur with triptans, including AMERGE,  
240 particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or  
241 serotonin norepinephrine reuptake inhibitors (SNRIs). Serotonin syndrome symptoms may  
242 include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g.,  
243 tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia,  
244 incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of  
245 symptoms can occur within minutes to hours of receiving a new or a greater dose of a  
246 serotonergic medication. Treatment with AMERGE should be discontinued if serotonin  
247 syndrome is suspected.

248 **Increase in Blood Pressure:** In healthy volunteers, dose-related increases in systemic blood  
249 pressure have been observed after administration of up to 20 mg of oral naratriptan. At the  
250 recommended doses, the elevations are generally small, although an increase of systolic pressure  
251 of 32 mmHg was seen in 1 patient following a single 2.5-mg dose. The effect may be more  
252 pronounced in the elderly and hypertensive patients. A patient who was mildly hypertensive (the  
253 baseline blood pressure was 150/98) experienced a significant increase in blood pressure to  
254 204/144 mmHg 225 minutes after administration of a 10-mg oral dose. Significant elevation in  
255 blood pressure, including hypertensive crisis, has been reported on rare occasions in patients  
256 receiving 5-HT<sub>1</sub> agonists with and without a history of hypertension. Naratriptan is  
257 contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS).

258 An 18% increase in mean pulmonary artery pressure and an 8% increase in mean aortic  
259 pressure was seen following dosing with 1.5 mg of subcutaneous naratriptan in a study  
260 evaluating 10 subjects with suspected CAD undergoing cardiac catheterization.

261 **Hypersensitivity:** Hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in  
262 patients receiving naratriptan. Such reactions can be life threatening or fatal. In general,  
263 hypersensitivity reactions to drugs are more likely to occur in individuals with a history of  
264 sensitivity to multiple allergens (see CONTRAINDICATIONS).

## 265 **PRECAUTIONS**

266 **General:** Chest discomfort (including pain, pressure, heaviness, tightness) has been reported  
267 after administration of 5-HT<sub>1</sub> agonists, including AMERGE Tablets. These events have not been  
268 associated with arrhythmias or ischemic ECG changes in clinical trials with AMERGE Tablets.  
269 Because naratriptan may cause coronary artery vasospasm, patients who experience signs or  
270 symptoms suggestive of angina following naratriptan should be evaluated for the presence of



271 CAD or a predisposition to Prinzmetal variant angina before receiving additional doses of  
272 naratriptan, and should be monitored electrocardiographically if dosing is resumed and similar  
273 symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of  
274 decreased arterial flow, such as ischemic bowel syndrome or Raynaud syndrome following  
275 naratriptan administration should be evaluated for atherosclerosis or predisposition to vasospasm  
276 (see CONTRAINDICATIONS and WARNINGS).

277 AMERGE Tablets should also be administered with caution to patients with diseases that may  
278 alter the absorption, metabolism, or excretion of drugs, such as impaired renal or hepatic  
279 function (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, and DOSAGE AND  
280 ADMINISTRATION).

281 Care should be taken to exclude other potentially serious neurological conditions before  
282 treating headache in patients not previously diagnosed with migraine or who experience a  
283 headache that is atypical for them. There have been rare reports where patients received 5-HT<sub>1</sub>  
284 agonists for severe headaches that were subsequently shown to have been secondary to an  
285 evolving neurologic lesion (see WARNINGS).

286 For a given attack, if a patient has no response to the first dose of AMERGE, the diagnosis of  
287 migraine should be reconsidered before administration of a second dose.

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

296 **Information for Patients:** See PATIENT INFORMATION at the end of the full prescribing  
297 information for the text of the separate leaflet provided for patients.

298 Patients should be cautioned about the risk of serotonin syndrome with the use of naratriptan  
299 or other triptans, especially during combined use with SSRIs or SNRIs.

300 **Laboratory Tests:** No specific laboratory tests are recommended for monitoring patients prior  
301 to and/or after treatment with AMERGE Tablets.

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

306 ***Ergot-Containing Drugs:*** Ergot-containing drugs have been reported to cause prolonged  
307 vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use  
308 of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide)  
309 and naratriptan within 24 hours is contraindicated (see CONTRAINDICATIONS).

310 **Other 5-HT<sub>1</sub> Agonists:** The administration of naratriptan with other 5-HT<sub>1</sub> agonists has not  
311 been evaluated in migraine patients. Because their vasospastic effects may be additive,  
312 coadministration of naratriptan and other 5-HT<sub>1</sub> agonists within 24 hours of each other is not  
313 recommended (see CONTRAINDICATIONS).

314 **Drug/Laboratory Test Interactions:** AMERGE Tablets are not known to interfere with  
315 commonly employed clinical laboratory tests.

316 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Lifetime  
317 carcinogenicity studies, 104 weeks in duration, were carried out in mice and rats by oral gavage.  
318 There was no evidence of an increase in tumors related to naratriptan administration in mice  
319 receiving up to 200 mg/kg/day. That dose was associated with a plasma area-under-the-curve  
320 (AUC) exposure that was 110 times the exposure in humans receiving the maximum  
321 recommended daily dose of 5 mg. Two rat studies were conducted, 1 using a standard diet and  
322 the other a nitrite-supplemented diet (naratriptan can be nitrosated in vitro to form a mutagenic  
323 product that has been detected in the stomachs of rats fed a high nitrite diet). Doses of 5, 20, and  
324 90 mg/kg were associated with week 13 AUC exposures that in the standard diet study were 7,  
325 40, and 236 times, respectively, and in the nitrite-supplemented diet study were 7, 29, and 180  
326 times, respectively, the exposure attained in humans given the maximum recommended daily  
327 dose of 5 mg. In both studies, there was an increase in the incidence of thyroid follicular  
328 hyperplasia in high-dose males and females and in thyroid follicular adenomas in high-dose  
329 males. In the standard diet study only, there was also an increase in the incidence of benign c-cell  
330 adenomas in the thyroid of high-dose males and females. The exposures achieved at the no-effect  
331 dose for thyroid tumors were 40 (standard diet) and 29 (nitrite-supplemented diet) times the  
332 exposure achieved in humans receiving the maximum recommended daily dose of 5 mg. In the  
333 nitrite-supplemented diet study only, the incidence of benign lymphocytic thymoma was  
334 increased in all treated groups of females. It was not determined if the nitrosated product is  
335 systemically absorbed. However, no changes were seen in the stomachs of rats in that study.

336 **Mutagenesis:** Naratriptan was not mutagenic when tested in 2 gene mutation assays, the  
337 Ames test and the in vitro thymidine locus mouse lymphoma assay. It was not clastogenic in 2  
338 cytogenetics assays, the in vitro human lymphocyte assay and the in vivo mouse micronucleus  
339 assay. Naratriptan can be nitrosated in vitro to form a mutagenic product (WHO nitrosation  
340 assay) that has been detected in the stomachs of rats fed a nitrite-supplemented diet.

341 **Impairment of Fertility:** In a reproductive toxicity study in which male and female rats  
342 were dosed prior to and throughout the mating period with 10, 60, 170, or 340 mg/kg/day  
343 (plasma exposures [AUC] approximately 11, 70, 230, and 470 times, respectively, the human  
344 exposure at the maximum recommended daily dose [MRDD] of 5 mg), there was a  
345 treatment-related decrease in the number of females exhibiting normal estrous cycles at doses of  
346 170 mg/kg/day or greater and an increase in preimplantation loss at 60 mg/kg/day or greater. In  
347 high-dose group males, testicular/epididymal atrophy accompanied by spermatozoa depletion  
348 reduced mating success and may have contributed to the observed preimplantation loss. The  
349 exposures achieved at the no-effect doses for preimplantation loss, anestrus, and testicular effects

350 were approximately 11, 70, and 230 times, respectively, the exposures in humans receiving the  
351 MRDD.

352 In a study in which rats were dosed orally with 10, 60, or 340 mg/kg/day for 6 months,  
353 changes in the female reproductive tract including atrophic or cystic ovaries and anestrus were  
354 seen at the high dose. The exposure at the no-effect dose of 60 mg/kg was approximately  
355 85 times the exposure in humans receiving the MRDD.

356 **Pregnancy:** Pregnancy Category C. There are no adequate and well-controlled studies in  
357 pregnant women; therefore, naratriptan should be used during pregnancy only if the potential  
358 benefit justifies the potential risk to the fetus.

359 To monitor fetal outcomes of pregnant women exposed to AMERGE, GlaxoSmithKline  
360 maintains a Naratriptan Pregnancy Registry. Healthcare providers are encouraged to register  
361 patients by calling (800) 336-2176.

362 In reproductive toxicity studies in rats and rabbits, oral administration of naratriptan was  
363 associated with developmental toxicity (embryo lethality, fetal abnormalities, pup mortality,  
364 offspring growth retardation) at doses producing maternal plasma drug exposures as low as 11  
365 and 2.5 times, respectively, the exposure in humans receiving the MRDD of 5 mg.

366 When pregnant rats were administered naratriptan during the period of organogenesis at doses  
367 of 10, 60, or 340 mg/kg/day, there was a dose-related increase in embryonic death, with a  
368 statistically significant difference at the highest dose, and incidences of fetal structural variations  
369 (incomplete/irregular ossification of skull bones, sternbrae, ribs) were increased at all doses.  
370 The maternal plasma exposures (AUC) at these doses were approximately 11, 70, and 470 times  
371 the exposure in humans at the MRDD. The high dose was maternally toxic, as evidenced by  
372 decreased maternal body weight gain during gestation. A no-effect dose for developmental  
373 toxicity in rats exposed during organogenesis was not established.

374 When doses of 1, 5, or 30 mg/kg/day were given to pregnant Dutch rabbits throughout  
375 organogenesis, the incidence of a specific fetal skeletal malformation (fused sternbrae) was  
376 increased at the high dose, and increased incidences of embryonic death and fetal variations  
377 (major blood vessel variations, supernumerary ribs, incomplete skeletal ossification) were  
378 observed at all doses (4, 20, and 120 times, respectively, the MRDD on a body surface area  
379 basis). Maternal toxicity (decreased body weight gain) was evident at the high dose in this study.  
380 In a similar study in New Zealand White rabbits (1, 5, or 30 mg/kg/day throughout  
381 organogenesis), decreased fetal weights and increased incidences of fetal skeletal variations were  
382 observed at all doses (maternal exposures equivalent to 2.5, 19, and 140 times exposure in  
383 humans receiving the MRDD), while maternal body weight gain was reduced at 5 mg/kg or  
384 greater. A no-effect dose for developmental toxicity in rabbits exposed during organogenesis was  
385 not established.

386 When female rats were treated with 10, 60, or 340 mg/kg/day during late gestation and  
387 lactation, offspring behavioral impairment (tremors) and decreased offspring viability and  
388 growth were observed at doses of 60 mg/kg or greater, while maternal toxicity occurred only at

389 the highest dose. Maternal exposures at the no-effect dose for developmental effects in this study  
390 were approximately 11 times the exposure in humans receiving the MRDD.

391 **Nursing Mothers:** Naratriptan-related material is excreted in the milk of rats. Therefore,  
392 caution should be exercised when considering the administration of AMERGE Tablets to a  
393 nursing woman.

394 **Pediatric Use:** Safety and effectiveness of AMERGE Tablets in pediatric patients (younger  
395 than 18 years) have not been established.

396 One randomized, placebo-controlled clinical trial evaluating oral naratriptan (0.25 to 2.5 mg)  
397 in pediatric patients aged 12 to 17 years evaluated a total of 300 adolescent migraineurs. This  
398 study did not establish the efficacy of oral naratriptan compared to placebo in the treatment of  
399 migraine in adolescents (see CLINICAL TRIALS). Adverse events observed in this clinical trial  
400 were similar in nature to those reported in clinical trials in adults.

401 **Geriatric Use:** The use of AMERGE Tablets in elderly patients is not recommended.

402 Naratriptan is known to be substantially excreted by the kidney, and the risk of adverse  
403 reactions to this drug may be greater in elderly patients who have reduced renal function. In  
404 addition, elderly patients are more likely to have decreased hepatic function; they are at higher  
405 risk for CAD; and blood pressure increases may be more pronounced in the elderly. Clinical  
406 studies of AMERGE Tablets did not include patients over 65 years of age.

## 407 **ADVERSE REACTIONS**

408 **Serious cardiac events, including some that have been fatal, have occurred following the**  
409 **use of 5-HT<sub>1</sub> agonists. These events are extremely rare and most have been reported in**  
410 **patients with risk factors predictive of CAD. Events reported have included coronary**  
411 **artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular**  
412 **tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and**  
413 **PRECAUTIONS).**

414 **Incidence in Controlled Clinical Trials:** The most common adverse events were  
415 paresthesias, dizziness, drowsiness, malaise/fatigue, and throat/neck symptoms, which occurred  
416 at a rate of 2% and at least 2 times placebo rate. Since patients treated only 1 to 3 headaches in  
417 the controlled clinical trials, the opportunity for discontinuation of therapy in response to an  
418 adverse event was limited. In a long-term, open-label study where patients were allowed to treat  
419 multiple migraine attacks for up to 1 year, 15 patients (3.6%) discontinued treatment due to  
420 adverse events.

421 Table 2 lists adverse events that occurred in 5 placebo-controlled clinical trials of  
422 approximately 1,752 exposures to placebo and AMERGE Tablets in adult migraine patients. The  
423 events cited reflect experience gained under closely monitored conditions of clinical trials in a  
424 highly selected patient population. In actual clinical practice or in other clinical trials, these  
425 frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of  
426 patients treated may differ. Only events that occurred at a frequency of 2% or more in the group  
427 treated with AMERGE Tablets 2.5 mg and were more frequent in that group than in the placebo

428 group are included in Table 2. From this table, it appears that many of these adverse events are  
429 dose related.

430

431 **Table 2. Treatment-Emergent Adverse Events Reported by at Least 2% of Patients in**  
432 **Placebo-Controlled Migraine Trials**

Adverse Event Type	Placebo (n = 498)	AMERGE 1 mg (n = 627)	AMERGE 2.5 mg (n = 627)
Atypical sensation	1%	2%	4%
Paresthesias (all types)	<1%	1%	2%
Gastrointestinal	5%	6%	7%
Nausea	4%	4%	5%
Neurological	3%	4%	7%
Dizziness	1%	1%	2%
Drowsiness	<1%	1%	2%
Malaise/fatigue	1%	2%	2%
Pain and pressure sensation	2%	2%	4%
Throat/neck symptoms	1%	1%	2%

433

434 One event (vomiting) present in more than 1% of patients receiving AMERGE Tablets  
435 occurred more frequently on placebo than on naratriptan 2.5 mg.

436 AMERGE Tablets are generally well tolerated. Most adverse reactions were mild and  
437 transient.

438 The incidence of adverse events in placebo-controlled clinical trials was not affected by age or  
439 weight of the patients, duration of headache prior to treatment, presence of aura, use of  
440 prophylactic medications, or tobacco use. There was insufficient data to assess the impact of race  
441 on the incidence of adverse events.

442 **Other Events Observed in Association With the Administration of AMERGE**

443 **Tablets:** In the paragraphs that follow, the frequencies of less commonly reported adverse  
444 clinical events are presented. Because the reports include events observed in open and  
445 uncontrolled studies, the role of AMERGE Tablets in their causation cannot be reliably  
446 determined. Furthermore, variability associated with adverse event reporting, the terminology  
447 used to describe adverse events, etc., limit the value of the quantitative frequency estimates  
448 provided. Event frequencies are calculated as the number of patients reporting an event divided  
449 by the total number of patients (n = 3,557) exposed to oral naratriptan doses up to 10 mg. All  
450 reported events are included except those already listed in the previous table, those too general to  
451 be informative, and those not reasonably associated with the use of the drug. Events are further  
452 classified within body system categories and enumerated in order of decreasing frequency using  
453 the following definitions: frequent adverse events are those occurring in at least 1/100 patients,  
454 infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, and rare adverse  
455 events are those occurring in fewer than 1/1,000 patients.



456 **Atypical Sensations:** Frequent were warm/cold temperature sensations. Infrequent were  
457 feeling strange and burning/stinging sensation.

458 **Cardiovascular:** Infrequent were palpitations, increased blood pressure, tachyarrhythmias,  
459 and abnormal ECG (PR prolongation, QT<sub>c</sub> prolongation, ST/T wave abnormalities, premature  
460 ventricular contractions, atrial flutter, or atrial fibrillation), and syncope. Rare were bradycardia,  
461 varicosities, hypotension, and heart murmurs.

462 **Ear, Nose, and Throat:** Frequent were ear, nose, and throat infections. Infrequent were  
463 phonophobia, sinusitis, upper respiratory inflammation, and tinnitus. Rare were allergic rhinitis;  
464 labyrinthitis; ear, nose, and throat hemorrhage; and hearing difficulty.

465 **Endocrine and Metabolic:** Infrequent were thirst and polydipsia, dehydration, and fluid  
466 retention. Rare were hyperlipidemia, hypercholesterolemia, hypothyroidism, hyperglycemia,  
467 glycosuria and ketonuria, and parathyroid neoplasm.

468 **Eye:** Frequent was photophobia. Infrequent was blurred vision. Rare were eye pain and  
469 discomfort, sensation of eye pressure, eye hemorrhage, dry eyes, difficulty focusing, and  
470 scotoma.

471 **Gastrointestinal:** Frequent were hyposalivation and vomiting. Infrequent were dyspeptic  
472 symptoms, diarrhea, gastrointestinal discomfort and pain, gastroenteritis, and constipation. Rare  
473 were abnormal liver function tests, abnormal bilirubin levels, hemorrhoids, gastritis, esophagitis,  
474 salivary gland inflammation, oral itching and irritation, regurgitation and reflux, and gastric  
475 ulcers.

476 **Hematological Disorders:** Infrequent was increased white cells. Rare were  
477 thrombocytopenia, quantitative red cell or hemoglobin defects, anemia, and purpura.

478 **Lower Respiratory Tract:** Infrequent were bronchitis, cough, and pneumonia. Rare were  
479 tracheitis, asthma, pleuritis, and airway constriction and obstruction.

480 **Musculoskeletal:** Infrequent were muscle pain, arthralgia and articular rheumatism, muscle  
481 cramps and spasms, joint and muscle stiffness, tightness, and rigidity. Rare were bone and  
482 skeletal pain.

483 **Neurological:** Frequent was vertigo. Infrequent were tremors, cognitive function disorders,  
484 sleep disorders, and disorders of equilibrium. Rare were compressed nerve syndromes,  
485 confusion, sedation, hyperesthesia, coordination disorders, paralysis of cranial nerves, decreased  
486 consciousness, dreams, altered sense of taste, neuralgia, neuritis, aphasia, hypoesthesia, motor  
487 retardation, muscle twitching and fasciculation, psychomotor restlessness, and convulsions.

488 **Non-Site Specific:** Infrequent were chills and/or fever, descriptions of odor or taste, edema  
489 and swelling, allergies, and allergic reactions. Rare were spasms and mobility disorders.

490 **Pain and Pressure Sensations:** Frequent were pressure/tightness/heaviness sensations.

491 **Psychiatry:** Infrequent were anxiety, depressive disorders, and detachment. Rare were  
492 aggression and hostility, agitation, hallucinations, panic, and hyperactivity.

493 **Reproduction:** Rare were lumps of female reproductive tract, breast inflammation,  
494 inflammation of vagina, inflammation of fallopian tube, breast discharge, endometrium  
495 disorders, decreased libido, and lumps of breast.



496 **Skin:** Infrequent were sweating, skin rashes, pruritus, and urticaria. Rare were skin erythema,  
497 dermatitis and dermatosis, hair loss and alopecia, pruritic skin rashes, acne and folliculitis,  
498 allergic skin reactions, macular skin/rashes, skin photosensitivity, photodermatitis, skin flakiness,  
499 and dry skin.

500 **Urology:** Infrequent were bladder inflammation and polyuria and diuresis. Rare were urinary  
501 tract hemorrhage, urinary urgency, pyelitis, and urinary incontinence.

502 **Observed During Clinical Practice:** The following section enumerates potentially important  
503 adverse events that have occurred in clinical practice and that have been reported spontaneously  
504 to various surveillance systems. The events enumerated represent reports arising from both  
505 domestic and nondomestic use of naratriptan. These events do not include those already listed in  
506 the ADVERSE REACTIONS section above. Because the reports cite events reported  
507 spontaneously from worldwide postmarketing experience, frequency of events and the role of  
508 naratriptan in their causation cannot be reliably determined.

509 **Cardiovascular:** Angina, myocardial infarction (see WARNINGS).

510 **Gastrointestinal:** Colonic ischemia (see WARNINGS).

511 **Lower Respiratory:** Dyspnea.

512 **Miscellaneous:** Hypersensitivity, including anaphylaxis/anaphylactoid reactions, in some  
513 cases severe (e.g., circulatory collapse) (see WARNINGS).

514 **Neurologic:** Cerebral vascular accident, including transient ischemic attack, subarachnoid  
515 hemorrhage, and cerebral infarction (see WARNINGS); serotonin syndrome.

## 516 **DRUG ABUSE AND DEPENDENCE**

517 In one clinical study enrolling 12 subjects, all of whom had experience using oral opiates and  
518 other psychoactive drugs, AMERGE Tablets produced less intense subjective responses  
519 ordinarily associated with many drugs of abuse than did codeine (30 to 90 mg).

## 520 **OVERDOSAGE**

521 A patient who was mildly hypertensive experienced a significant increase in blood pressure  
522 after administration of a 10-mg dose starting at 30 minutes (baseline value of 150/98 to  
523 204/144 mmHg 225 minutes). This event resolved after treatment with antihypertensive therapy.  
524 Oral administration of 25 mg of naratriptan in 1 healthy young male subject increased blood  
525 pressure from 120/67 mmHg pretreatment up to 191/113 mmHg at approximately 6 hours  
526 postdose and resulted in adverse events including lightheadedness, tension in the neck, tiredness,  
527 and loss of coordination. Blood pressure returned to near baseline by 8 hours after dosing  
528 without any pharmacological intervention.

529 Another subject experienced asymptomatic ischemic ECG changes likely due to coronary  
530 artery vasospasm approximately 2 hours following a 7.5-mg oral dose.

531 The elimination half-life of naratriptan is about 6 hours (see CLINICAL  
532 PHARMACOLOGY), and therefore monitoring of patients after overdose with AMERGE  
533 Tablets should continue for at least 24 hours or while symptoms or signs persist. There is no  
534 specific antidote to naratriptan. Standard supportive treatment should be applied as required. If

535 the patient presents with chest pain or other symptoms consistent with angina pectoris, ECG  
536 monitoring should be performed for evidence of ischemia. It is unknown what effect  
537 hemodialysis or peritoneal dialysis has on the serum concentrations of naratriptan.

## 538 **DOSAGE AND ADMINISTRATION**

539 In controlled clinical trials, single doses of 1 and 2.5 mg of AMERGE Tablets taken with fluid  
540 were effective for the acute treatment of migraines in adults. A greater proportion of patients had  
541 headache response following a 2.5-mg dose than following a 1-mg dose (see CLINICAL  
542 TRIALS). Individuals may vary in response to doses of AMERGE Tablets. The choice of dose  
543 should therefore be made on an individual basis, weighing the possible benefit of the 2.5-mg  
544 dose with the potential for a greater risk of adverse events. If the headache returns or if the  
545 patient has only partial response, the dose may be repeated once after 4 hours, for a maximum  
546 dose of 5 mg in a 24-hour period. There is evidence that doses of 5 mg do not provide a greater  
547 effect than 2.5 mg.

548 The safety of treating, on average, more than 4 headaches in a 30-day period has not been  
549 established.

550 **Renal Impairment:** The use of AMERGE is contraindicated in patients with severe renal  
551 impairment (creatinine clearance, <15 mL/min) because of decreased clearance of the drug (see  
552 CONTRAINDICATIONS and CLINICAL PHARMACOLOGY). In patients with mild to  
553 moderate renal impairment, the maximum daily dose should not exceed 2.5 mg over a 24-hour  
554 period and a lower starting dose should be considered.

555 **Hepatic Impairment:** The use of AMERGE is contraindicated in patients with severe hepatic  
556 impairment (Child-Pugh grade C) because of decreased clearance (see CONTRAINDICATIONS  
557 and CLINICAL PHARMACOLOGY). In patients with mild or moderate hepatic impairment, the  
558 maximum daily dose should not exceed 2.5 mg over a 24-hour period and a lower starting dose  
559 should be considered (see CLINICAL PHARMACOLOGY).

## 560 **HOW SUPPLIED**

561 AMERGE Tablets 1 and 2.5 mg of naratriptan (base) as the hydrochloride. AMERGE Tablets,  
562 1 mg, are white, D-shaped, film-coated tablets debossed with “GX CE3” on one side in blister  
563 packs of 9 tablets (NDC 0173-0561-00). AMERGE Tablets, 2.5 mg, are green, D-shaped,  
564 film-coated tablets debossed with “GX CE5” on one side in blister packs of 9 tablets (NDC  
565 0173-0562-00).

566 **Store at controlled room temperature, 20° to 25°C (68° to 77°F) (see USP).**  
567  
568



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## 577 **PATIENT INFORMATION**

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

579

580 **Patient Information**

581 **AMERGE® (a-MERJ)**

582 **(naratriptan hydrochloride)**

583 **Tablets**

584

585 Read this Patient Information before you start taking AMERGE and each time you get a refill.

586 There may be new information. This information does not take the place of talking with your

587 healthcare provider about your medical condition or treatment.

588

589 **What is the most important information I should know about AMERGE?**

590 **AMERGE can cause serious side effects, including:**

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

592 **Stop taking AMERGE and get emergency medical help right away if you have any of the**  
593 **following symptoms of a heart attack:**

- 594 • discomfort in the center of your chest that lasts for more than a few minutes, or that goes  
595 away and comes back.
- 596 • chest pain or chest discomfort that feels like heavy pressure, squeezing, or fullness
- 597 • pain or discomfort in your arms, back, neck, jaw, or stomach
- 598 • shortness of breath with or without chest discomfort
- 599 • breaking out in a cold sweat
- 600 • nausea or vomiting
- 601 • feeling lightheaded

602 AMERGE is not for people with risk factors for heart disease unless a heart exam is done and  
603 shows no problem. You have a higher risk for heart disease if you:

- 604 • have high blood pressure
- 605 • have high cholesterol levels
- 606 • smoke
- 607 • are overweight
- 608 • have diabetes
- 609 • have a family history of heart disease

- 610 • are a female who has gone through menopause
- 611 • are a male over age 40

612 **Serotonin syndrome.** Serotonin syndrome is a serious and life-threatening problem that can  
613 happen in people taking AMERGE, especially if AMERGE is used with anti-depressant  
614 medicines called selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine  
615 reuptake inhibitors (SNRIs).

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

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

- 619 • mental changes such as seeing things that are not there (hallucinations), agitation, or coma
- 620 • fast heartbeat
- 621 • changes in blood pressure
- 622 • high body temperature
- 623 • tight muscles
- 624 • trouble walking
- 625 • nausea, vomiting, or diarrhea

626

#### 627 **What is AMERGE?**

628 AMERGE is a prescription medicine used to treat acute migraine headaches with or without aura  
629 in adults.

630 AMERGE is not used to prevent or decrease the number of migraine headaches you have.

631 AMERGE is not used to treat other types of headaches such as hemiplegic migraines (that make  
632 you unable to move on one side of your body) or basilar migraines (rare form of migraine with  
633 aura).

634 It is not known if AMERGE is safe and effective to treat cluster headaches.

635 It is not known if AMERGE is safe and effective in children under 18 years of age.

636

#### 637 **Who should not take AMERGE?**

##### 638 **Do not take AMERGE if you have:**

- 639 • heart problems or a history of heart problems
- 640 • narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular  
641 disease)
- 642 • uncontrolled high blood pressure
- 643 • severe kidney problems
- 644 • severe liver problems
- 645 • hemiplegic migraines or basilar migraines. If you are not sure if you have these types of  
646 migraines, ask your healthcare provider.

- 647 • had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation
- 648 • taken any of the following medicines in the last 24 hours:
  - 649 • almotriptan (AXERT<sup>®</sup>)
  - 650 • eletriptan (RELPAX<sup>®</sup>)
  - 651 • frovatriptan (FROVA<sup>®</sup>)
  - 652 • rizatriptan (MAXALT<sup>®</sup>, MAXALT-MLT<sup>®</sup>)
  - 653 • sumatriptan (IMITREX<sup>®</sup>, SUMAVEL<sup>®</sup> DosePro<sup>®</sup>)
  - 654 • sumatriptan and naproxen (TREXIMET<sup>®</sup>)
  - 655 • ergotamines (CAFERGOT<sup>®</sup>, ERGOMAR<sup>®</sup>, MIGERGOT<sup>®</sup>)
  - 656 • dihydroergotamine (D.H.E. 45<sup>®</sup>, MIGRANAL<sup>®</sup>)
- 657 Ask your doctor if you are not sure if your medicine is listed above.
- 658 • an allergy to naratriptan hydrochloride or any of the ingredients in AMERGE. See the end of
- 659 this leaflet for a complete list of ingredients in AMERGE.

660

### 661 **What should I tell my healthcare provider before taking AMERGE?**

662 Before you take AMERGE, tell your healthcare provider about all of your medical conditions,  
663 including if you:

- 664 • have high blood pressure
- 665 • have high cholesterol
- 666 • have diabetes
- 667 • smoke
- 668 • are overweight
- 669 • are a female who has gone through menopause
- 670 • have heart disease or a family history of heart disease or stroke
- 671 • have kidney problems
- 672 • have liver problems
- 673 • have had epilepsy or seizures
- 674 • are not using effective birth control
- 675 • are pregnant or plan to become pregnant. It is not known if AMERGE will harm your unborn  
676 baby.
- 677 • become pregnant while taking AMERGE. Talk with your healthcare provider about  
678 registering with the Naratriptan Pregnancy Registry. Your healthcare provider can enroll you  
679 in this registry by calling 1-800-336-2176.
- 680 • are breastfeeding or plan to breastfeed. AMERGE passes into your breast milk and may harm  
681 your baby. Talk with your healthcare provider about the best way to feed your baby if you  
682 take AMERGE.

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

685 AMERGE and other medicines may affect each other, causing side effects.

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

- 687 • selective serotonin reuptake inhibitors (SSRIs)
- 688 • serotonin norepinephrine reuptake inhibitors (SNRIs)
- 689 • monoamine oxidase inhibitors (MAOIs)

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

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

693

#### 694 **How should I take AMERGE?**

- 695 • Certain people should take their first dose of AMERGE in their healthcare provider's office  
696 or in another medical setting. Ask your healthcare provider if you should take your first dose  
697 in a medical setting.
- 698 • Take AMERGE exactly as your healthcare provider tells you to take it.
- 699 • Your healthcare provider may change your dose. Do not change your dose without first  
700 talking with your healthcare provider.
- 701 • Take AMERGE with water or other liquids.
- 702 • If you do not get any relief after your first AMERGE tablet, do not take a second tablet  
703 without first talking with your healthcare provider.
- 704 • If your headache comes back or you only get some relief from your headache, you can take a  
705 second tablet 4 hours after the first tablet.
- 706 • Do not take more than a total of 5 mg of AMERGE in a 24-hour period.
- 707 • Some people who take too many AMERGE tablets may have worse headaches (medication  
708 overuse headache). If your headaches get worse, your healthcare provider may decide to stop  
709 your treatment with AMERGE.
- 710 • If you take too much AMERGE, call your healthcare provider or go to the nearest hospital  
711 emergency room right away.
- 712 • You should write down when you have headaches and when you take AMERGE so you can  
713 talk with your healthcare provider about how AMERGE is working for you.

714

#### 715 **What should I avoid while taking AMERGE?**

716 AMERGE can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not  
717 drive a car, use machinery, or do anything where you need to be alert.

718

#### 719 **What are the possible side effects of AMERGE?**

720 **AMERGE may cause serious side effects.** See “What is the most important information I  
721 should know about AMERGE?”

722 These serious side effects include:

- 723 • changes in color or sensation in your fingers and toes (Raynaud's syndrome)



- 724 • stomach and intestinal problems (gastrointestinal and colonic ischemic events). Symptoms of  
725 gastrointestinal and colonic ischemic events include:
- 726 • sudden or severe stomach pain
  - 727 • stomach pain after meals
  - 728 • weight loss
  - 729 • nausea or vomiting
  - 730 • constipation or diarrhea
  - 731 • bloody diarrhea
  - 732 • fever
- 733 • problems with blood circulation to your legs and feet (peripheral vascular ischemia).  
734 Symptoms of peripheral vascular ischemia include:
- 735 • cramping and pain in your legs or hips
  - 736 • feeling of heaviness or tightness in your leg muscles
  - 737 • burning or aching pain in your feet or toes while resting
  - 738 • numbness, tingling, or weakness in your legs
  - 739 • cold feeling or color changes in 1 or both legs or feet
  - 740 • shortness of breath or wheezing
  - 741 • hives (itchy bumps); swelling of your tongue, mouth, or throat
- 742 The most common side effects of AMERGE include:
- 743 • dizziness
  - 744 • warm, hot, burning feeling to your face (flushing)
  - 745 • cold and hot temperature sensations
  - 746 • sensitivity to light or vision problems
  - 747 • ear, nose, and throat infections
  - 748 • feeling weak, drowsy, or tired
  - 749 • decrease in saliva
- 750 Tell your healthcare provider if you have any side effect that bothers you or that does not go  
751 away.
- 752 These are not all the possible side effects of AMERGE. For more information, ask your  
753 healthcare provider or pharmacist.
- 754 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-  
755 800-FDA-1088.
- 756
- 757 **How should I store AMERGE?**
- 758 Store AMERGE between 68°F to 77°F (20°C to 25°C).
- 759 **Keep AMERGE and all medicines out of the reach of children.**
- 760

761 **General information about the safe and effective use of AMERGE.**

762 Medicines are sometimes prescribed for purposes other than those listed in Patient Information  
763 leaflets. Do not use AMERGE for a condition for which it was not prescribed. Do not give  
764 AMERGE to other people, even if they have the same symptoms you have. It may harm them.

765 This Patient Information leaflet summarizes the most important information about AMERGE. If  
766 you would like more information, talk with your healthcare provider. You can ask your  
767 healthcare provider or pharmacist for information about AMERGE that is written for healthcare  
768 professionals.

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

770

771 **What are the ingredients in AMERGE?**

772 Active ingredient: naratriptan hydrochloride

773 Inactive ingredients: croscarmellose sodium, hypromellose, lactose, magnesium stearate,  
774 microcrystalline cellulose, triacetin, titanium dioxide

775 2.5-mg tablets also contain iron oxide yellow and indigo carmine aluminum lake (FD&C Blue  
776 No. 2) for coloring.

777

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779 other brands listed are trademarks of their respective owners and are not trademarks of  
780 GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse  
781 GlaxoSmithKline or its products.

782

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

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