

## PRESCRIBING INFORMATION

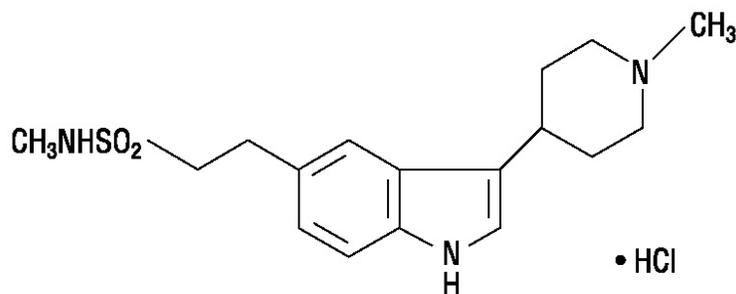
# AMERGE<sup>®</sup>

## (natriptan hydrochloride)

### Tablets

#### DESCRIPTION

AMERGE Tablets contain naratriptan as the hydrochloride, which is a selective 5-hydroxytryptamine<sub>1</sub> receptor subtype agonist. Naratriptan 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. Naratriptan 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 naratriptan hydrochloride equivalent to 1 or 2.5 mg of naratriptan, 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:** Naratriptan 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 naratriptan 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, naratriptan 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. Naratriptan 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  
65 (Child-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%* (n = 117)	60%* (n = 127)
Study 2	27% (n = 104)	52%* (n = 208)	66%*† (n = 199)
Study 3	32% (n = 169)	54%* (n = 166)	65%* (n = 167)

103 \*p<0.05 in comparison with placebo.

104 †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.

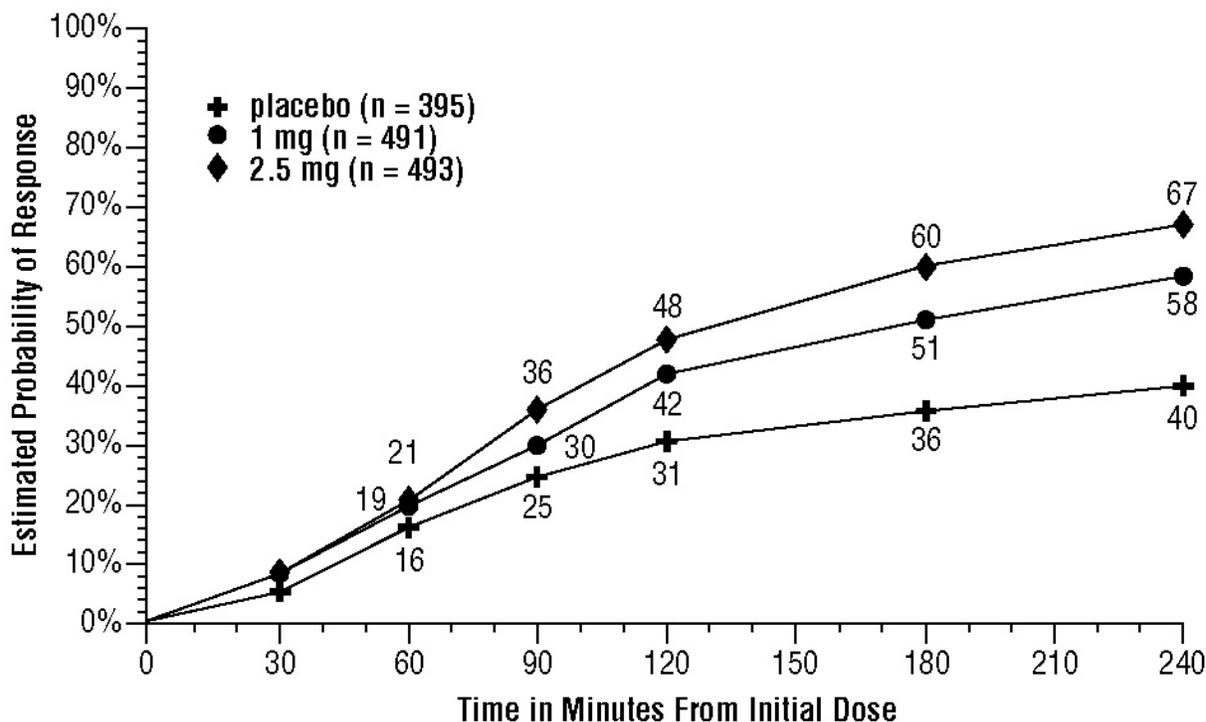
109 **Comparisons of drug performance based upon results obtained in different clinical trials**  
110 **are never reliable. Because studies are conducted at different times, with different samples**  
111 **of patients, by different investigators, employing different criteria and/or different**  
112 **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 4 Hours\***

119



120

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

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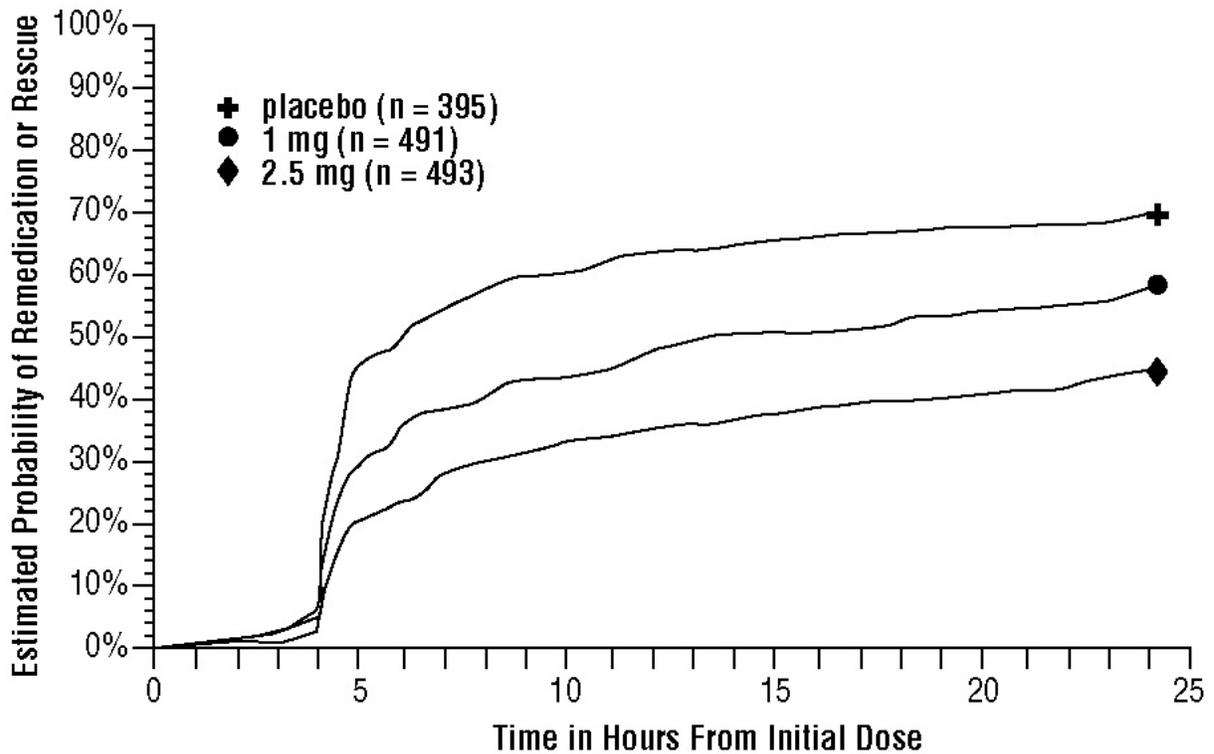
127 For patients with migraine-associated nausea, photophobia, and phonophobia at baseline,  
128 there was a lower incidence of these symptoms 4 hours following administration of 1- and  
129 2.5-mg AMERGE Tablets compared to placebo.

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

135

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

139



140

141 \* Kaplan-Meier plot based on data obtained in the 3 controlled clinical trials (Studies 1, 2, and  
142 3) providing evidence of efficacy with patients not using additional treatments censored at  
143 24 hours. The plot also includes patients who had no response to the initial dose.

144 Remedication was discouraged prior to 4 hours postdose.

145

146 There is no evidence that doses of 5 mg provide a greater effect than 2.5 mg. There was no  
147 evidence to suggest that treatment with AMERGE was associated with an increase in the severity  
148 or frequency of migraine attacks. The efficacy of AMERGE Tablets was unaffected by presence

149 of aura; gender, age, or weight of the patient; oral contraceptive use; or concomitant use of  
150 common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic  
151 antidepressants). There was insufficient data to assess the impact of race on efficacy.

## 152 **INDICATIONS AND USAGE**

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

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

## 159 **CONTRAINDICATIONS**

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

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

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

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

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

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

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

## 184 **WARNINGS**

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

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

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

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

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

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

223 ***Premarketing Experience With AMERGE Tablets:*** Among approximately 3,500  
224 patients with migraine who participated in premarketing clinical trials of naratriptan tablets,  
225 4 patients treated with single oral doses of naratriptan ranging from 1 to 10 mg experienced

226 asymptomatic ischemic ECG changes with at least 1, who took 7.5 mg, likely due to coronary  
227 vasospasm.

228 **Cerebrovascular Events and Fatalities With 5-HT<sub>1</sub> Agonists:** Cerebral hemorrhage,  
229 subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in  
230 patients treated with 5-HT<sub>1</sub> agonists, and some have resulted in fatalities. In a number of cases, it  
231 appears possible that the cerebrovascular events were primary, the agonist having been  
232 administered in the incorrect belief that the symptoms experienced were a consequence of  
233 migraine, when they were not. It should be noted that patients with migraine may be at increased  
234 risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

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

238 **Serotonin Syndrome:** The development of a potentially life-threatening serotonin syndrome  
239 may occur with triptans, including treatment with AMERGE, particularly during combined use  
240 with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake  
241 inhibitors (SNRIs). If concomitant treatment with naratriptan and an SSRI (e.g., fluoxetine,  
242 paroxetine, sertraline, fluvoxamine, citalopram, escitalopram) or SNRI (e.g., venlafaxine,  
243 duloxetine) is clinically warranted, careful observation of the patient is advised, particularly  
244 during treatment initiation and dose increases. Serotonin syndrome symptoms may include  
245 mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g.,  
246 tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia,  
247 incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

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 **Binding to Melanin-Containing Tissues:** In rats treated with a single oral dose (10 mg/kg)  
289 of radiolabeled naratriptan, the elimination half-life of radioactivity from the eye was 90 days,  
290 suggesting that naratriptan and/or its metabolites may bind to the melanin of the eye. Because  
291 there could be accumulation in melanin-rich tissues over time, this raises the possibility that  
292 naratriptan could cause toxicity in these tissues after extended use. Although no systematic  
293 monitoring of ophthalmologic function was undertaken in clinical trials, and no specific  
294 recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the  
295 possibility of long-term ophthalmologic effects.

296 **Changes in the Precorneal Tear Film:** Dogs receiving oral naratriptan showed transient  
297 changes in the precorneal tear film. Corneal stippling was seen at the lowest dose tested,  
298 1 mg/kg/day, and occurred intermittently from day 1 throughout the first 2 to 3 weeks of  
299 treatment. Although a no-effect dose was not established, the exposure at the lowest dose tested  
300 was approximately 5 times the human exposure after a 5-mg oral dose.

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

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

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

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

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

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

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

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

341 ***Mutagenesis:*** Naratriptan was not mutagenic when tested in 2 gene mutation assays, the  
342 Ames test and the in vitro thymidine locus mouse lymphoma assay. It was not clastogenic in 2  
343 cytogenetics assays, the in vitro human lymphocyte assay and the in vivo mouse micronucleus

344 assay. Naratriptan can be nitrosated in vitro to form a mutagenic product (WHO nitrosation  
345 assay) that has been detected in the stomachs of rats fed a nitrite-supplemented diet.

346 **Impairment of Fertility:** In a reproductive toxicity study in which male and female rats  
347 were dosed prior to and throughout the mating period with 10, 60, 170, or 340 mg/kg/day  
348 (plasma exposures [AUC] approximately 11, 70, 230, and 470 times, respectively, the human  
349 exposure at the maximum recommended daily dose [MRDD] of 5 mg), there was a  
350 treatment-related decrease in the number of females exhibiting normal estrous cycles at doses of  
351 170 mg/kg/day or greater and an increase in preimplantation loss at 60 mg/kg/day or greater. In  
352 high-dose group males, testicular/epididymal atrophy accompanied by spermatozoa depletion  
353 reduced mating success and may have contributed to the observed preimplantation loss. The  
354 exposures achieved at the no-effect doses for preimplantation loss, anestrus, and testicular effects  
355 were approximately 11, 70, and 230 times, respectively, the exposures in humans receiving the  
356 MRDD.

357 In a study in which rats were dosed orally with 10, 60, or 340 mg/kg/day for 6 months,  
358 changes in the female reproductive tract including atrophic or cystic ovaries and anestrus were  
359 seen at the high dose. The exposure at the no-effect dose of 60 mg/kg was approximately  
360 85 times the exposure in humans receiving the MRDD.

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

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

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

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

379 When doses of 1, 5, or 30 mg/kg/day were given to pregnant Dutch rabbits throughout  
380 organogenesis, the incidence of a specific fetal skeletal malformation (fused sternebrae) was  
381 increased at the high dose, and increased incidences of embryonic death and fetal variations  
382 (major blood vessel variations, supernumerary ribs, incomplete skeletal ossification) were  
383 observed at all doses (4, 20, and 120 times, respectively, the MRDD on a body surface area

384 basis). Maternal toxicity (decreased body weight gain) was evident at the high dose in this study.  
385 In a similar study in New Zealand White rabbits (1, 5, or 30 mg/kg/day throughout  
386 organogenesis), decreased fetal weights and increased incidences of fetal skeletal variations were  
387 observed at all doses (maternal exposures equivalent to 2.5, 19, and 140 times exposure in  
388 humans receiving the MRDD), while maternal body weight gain was reduced at 5 mg/kg or  
389 greater. A no-effect dose for developmental toxicity in rabbits exposed during organogenesis was  
390 not established.

391 When female rats were treated with 10, 60, or 340 mg/kg/day during late gestation and  
392 lactation, offspring behavioral impairment (tremors) and decreased offspring viability and  
393 growth were observed at doses of 60 mg/kg or greater, while maternal toxicity occurred only at  
394 the highest dose. Maternal exposures at the no-effect dose for developmental effects in this study  
395 were approximately 11 times the exposure in humans receiving the MRDD.

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

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

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

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

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

## 412 **ADVERSE REACTIONS**

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

419 **Incidence in Controlled Clinical Trials:** The most common adverse events were  
420 paresthesias, dizziness, drowsiness, malaise/fatigue, and throat/neck symptoms, which occurred  
421 at a rate of 2% and at least 2 times placebo rate. Since patients treated only 1 to 3 headaches in  
422 the controlled clinical trials, the opportunity for discontinuation of therapy in response to an

423 adverse event was limited. In a long-term, open-label study where patients were allowed to treat  
424 multiple migraine attacks for up to 1 year, 15 patients (3.6%) discontinued treatment due to  
425 adverse events.

426 Table 2 lists adverse events that occurred in 5 placebo-controlled clinical trials of  
427 approximately 1,752 exposures to placebo and AMERGE Tablets in adult migraine patients. The  
428 events cited reflect experience gained under closely monitored conditions of clinical trials in a  
429 highly selected patient population. In actual clinical practice or in other clinical trials, these  
430 frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of  
431 patients treated may differ. Only events that occurred at a frequency of 2% or more in the group  
432 treated with AMERGE Tablets 2.5 mg and were more frequent in that group than in the placebo  
433 group are included in Table 2. From this table, it appears that many of these adverse events are  
434 dose related.

435

436 **Table 2. Treatment-Emergent Adverse Events Reported by at Least 2% of Patients in**  
437 **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%

438

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

441 AMERGE Tablets are generally well tolerated. Most adverse reactions were mild and  
442 transient.

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

447 **Other Events Observed in Association With the Administration of AMERGE**  
448 **Tablets:** In the paragraphs that follow, the frequencies of less commonly reported adverse  
449 clinical events are presented. Because the reports include events observed in open and  
450 uncontrolled studies, the role of AMERGE Tablets in their causation cannot be reliably

451 determined. Furthermore, variability associated with adverse event reporting, the terminology  
452 used to describe adverse events, etc., limit the value of the quantitative frequency estimates  
453 provided. Event frequencies are calculated as the number of patients reporting an event divided  
454 by the total number of patients (n = 3,557) exposed to oral naratriptan doses up to 10 mg. All  
455 reported events are included except those already listed in the previous table, those too general to  
456 be informative, and those not reasonably associated with the use of the drug. Events are further  
457 classified within body system categories and enumerated in order of decreasing frequency using  
458 the following definitions: frequent adverse events are those occurring in at least 1/100 patients,  
459 infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, and rare adverse  
460 events are those occurring in fewer than 1/1,000 patients.

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

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

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

470 **Endocrine and Metabolic:** Infrequent were thirst and polydipsia, dehydration, and fluid  
471 retention. Rare were hyperlipidemia, hypercholesterolemia, hypothyroidism, hyperglycemia,  
472 glycosuria and ketonuria, and parathyroid neoplasm.

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

476 **Gastrointestinal:** Frequent were hyposalivation and vomiting. Infrequent were dyspeptic  
477 symptoms, diarrhea, gastrointestinal discomfort and pain, gastroenteritis, and constipation. Rare  
478 were abnormal liver function tests, abnormal bilirubin levels, hemorrhoids, gastritis, esophagitis,  
479 salivary gland inflammation, oral itching and irritation, regurgitation and reflux, and gastric  
480 ulcers.

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

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

485 **Musculoskeletal:** Infrequent were muscle pain, arthralgia and articular rheumatism, muscle  
486 cramps and spasms, joint and muscle stiffness, tightness, and rigidity. Rare were bone and  
487 skeletal pain.

488 **Neurological:** Frequent was vertigo. Infrequent were tremors, cognitive function disorders,  
489 sleep disorders, and disorders of equilibrium. Rare were compressed nerve syndromes,  
490 confusion, sedation, hyperesthesia, coordination disorders, paralysis of cranial nerves, decreased

491 consciousness, dreams, altered sense of taste, neuralgia, neuritis, aphasia, hypoesthesia, motor  
492 retardation, muscle twitching and fasciculation, psychomotor restlessness, and convulsions.

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

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

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

498 **Reproduction:** Rare were lumps of female reproductive tract, breast inflammation,  
499 inflammation of vagina, inflammation of fallopian tube, breast discharge, endometrium  
500 disorders, decreased libido, and lumps of breast.

501 **Skin:** Infrequent were sweating, skin rashes, pruritus, and urticaria. Rare were skin erythema,  
502 dermatitis and dermatosis, hair loss and alopecia, pruritic skin rashes, acne and folliculitis,  
503 allergic skin reactions, macular skin/rashes, skin photosensitivity, photodermatitis, skin flakiness,  
504 and dry skin.

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

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

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

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

516 **Lower Respiratory:** Dyspnea.

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

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

## 521 **DRUG ABUSE AND DEPENDENCE**

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

## 525 **OVERDOSAGE**

526 A patient who was mildly hypertensive experienced a significant increase in blood pressure  
527 after administration of a 10-mg dose starting at 30 minutes (baseline value of 150/98 to  
528 204/144 mmHg 225 minutes). This event resolved after treatment with antihypertensive therapy.  
529 Oral administration of 25 mg of naratriptan in 1 healthy young male subject increased blood

530 pressure from 120/67 mmHg pretreatment up to 191/113 mmHg at approximately 6 hours  
531 postdose and resulted in adverse events including lightheadedness, tension in the neck, tiredness,  
532 and loss of coordination. Blood pressure returned to near baseline by 8 hours after dosing  
533 without any pharmacological intervention.

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

536 The elimination half-life of naratriptan is about 6 hours (see CLINICAL  
537 PHARMACOLOGY), and therefore monitoring of patients after overdose with AMERGE  
538 Tablets should continue for at least 24 hours or while symptoms or signs persist. There is no  
539 specific antidote to naratriptan. Standard supportive treatment should be applied as required. If  
540 the patient presents with chest pain or other symptoms consistent with angina pectoris, ECG  
541 monitoring should be performed for evidence of ischemia. It is unknown what effect  
542 hemodialysis or peritoneal dialysis has on the serum concentrations of naratriptan.

## 543 **DOSAGE AND ADMINISTRATION**

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

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

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

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

## 565 **HOW SUPPLIED**

566 AMERGE Tablets 1 and 2.5 mg of naratriptan (base) as the hydrochloride. AMERGE Tablets,  
567 1 mg, are white, D-shaped, film-coated tablets debossed with “GX CE3” on one side in blister  
568 packs of 9 tablets (NDC 0173-0561-00). AMERGE Tablets, 2.5 mg, are green, D-shaped,

569 film-coated tablets debossed with “GX CE5” on one side in blister packs of 9 tablets (NDC  
570 0173-0562-00).

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

## 572 **PATIENT INFORMATION**

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

574

### 575 **Information for the Patient**

#### 576 **AMERGE<sup>®\*</sup> (naratriptan hydrochloride) Tablets**

577

578 Please read this leaflet carefully before you take AMERGE Tablets. This leaflet provides a  
579 summary of the information available about your medicine. Please do not throw away this leaflet  
580 until you have finished your medicine. You may need to read this leaflet again. This leaflet does  
581 not contain all the information on AMERGE Tablets. For further information or advice, ask your  
582 doctor or pharmacist.

#### 583 **Information About Your Medicine:**

584 The name of your medicine is AMERGE (naratriptan hydrochloride) Tablets. It can be  
585 obtained only by prescription from your doctor. The decision to use AMERGE Tablets is one  
586 that you and your doctor should make jointly, taking into account your individual preferences  
587 and medical circumstances. If you have risk factors for heart disease (such as high blood  
588 pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or  
589 you are postmenopausal or a male over 40), you should tell your doctor, who should evaluate  
590 you for heart disease in order to determine if AMERGE is appropriate for you. The majority of  
591 those who have taken AMERGE Tablets have not experienced any significant side effects.  
592 Rarely, deaths and/or serious heart problems have been reported with this class of medicines; in  
593 all but a few instances, however, these deaths and/or serious heart problems occurred in people  
594 with heart disease and it was not clear whether these medicines were a contributing factor.

#### 595 **1. The Purpose of Your Medicine:**

596 AMERGE Tablets are intended to relieve your migraine, but not to prevent or reduce the  
597 number of attacks you experience. Use AMERGE Tablets only to treat an actual migraine attack.

#### 598 **2. Important Questions to Consider Before Taking AMERGE Tablets:**

599 If the answer to any of the following questions is **YES** or if you do not know the answer, then  
600 please discuss it with your doctor before you use AMERGE Tablets.

- 601 • Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant?  
602 Are you not using adequate contraception? Are you breastfeeding?
- 603 • Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have  
604 you had a heart attack?
- 605 • Do you have risk factors for heart disease (such as high blood pressure, high cholesterol,  
606 obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal  
607 or a male over 40)?

- 608 • Have you had a stroke, transient ischemic attacks (TIAs), or Raynaud syndrome?  
609 • Do you have high blood pressure?  
610 • Have you ever had to stop taking this or any other medicine because of an allergy or other  
611 problems?  
612 • Are you taking any other migraine medicines, including other 5-HT<sub>1</sub> agonists such as  
613 IMITREX<sup>®</sup>\* (sumatriptan/sumatriptan succinate), or medicines containing ergotamine,  
614 dihydroergotamine, or methysergide?  
615 • Are you taking any medicine for depression or other disorders such as selective serotonin  
616 reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)?  
617 Common SSRIs are citalopram HBr (CELEXA<sup>®</sup>), escitalopram oxalate (LEXAPRO<sup>®</sup>),  
618 paroxetine (PAXIL<sup>®</sup>), fluoxetine (PROZAC<sup>®</sup>/SARAFEM<sup>®</sup>), olanzapine/fluoxetine  
619 (SYMBYAX<sup>®</sup>), sertraline (ZOLOFT<sup>®</sup>), and fluvoxamine. Common SNRIs are duloxetine  
620 (CYMBALTA<sup>®</sup>) and venlafaxine (EFFEXOR<sup>®</sup>).\*  
621 • Have you had, or do you have, any disease of the kidney or liver?  
622 • Is this headache different from your usual migraine attacks?

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

### 625 ***3. The Use of AMERGE Tablets During Pregnancy:***

626 Do not use AMERGE Tablets if you are pregnant, think you might be pregnant, are trying to  
627 become pregnant, or are not using adequate contraception, unless you have discussed this with  
628 your doctor.

### 629 ***4. How to Use AMERGE Tablets:***

630 For adults, the usual dose is a single tablet taken whole with fluids. It may be given at any  
631 time after the headache starts. For an individual attack, if you have no response to the first tablet,  
632 do not take a second tablet without first talking to your doctor. If you need more relief due to a  
633 partial response or return of your headache after the first tablet, a second tablet may be taken, but  
634 not sooner than 4 hours following the first tablet. Do not take more than a total of 2 AMERGE  
635 Tablets in any 24-hour period. If you have kidney or liver disease, take as directed by your  
636 doctor.

### 637 ***5. Side Effects to Watch for:***

- 638 • Some patients experience pain or tightness in the chest or throat when using AMERGE  
639 Tablets. If this happens to you, then discuss it with your doctor before using any more  
640 AMERGE Tablets. If the chest pain, tightness, or pressure is severe or does not go away, call  
641 your doctor immediately.  
642 • If you have sudden and/or severe abdominal pain following AMERGE Tablets, call your  
643 doctor immediately.  
644 • Some people may have a reaction called serotonin syndrome when they use certain types of  
645 antidepressants, SSRIs or SNRIs, while taking AMERGE Tablets. Symptoms may include  
646 confusion, hallucinations, fast heart beat, feeling faint, fever, sweating, muscle spasm,

647 difficulty walking, and/or diarrhea. Call your doctor immediately if you have any of these  
648 symptoms after taking AMERGE Tablets.

- 649 • Shortness of breath; wheeziness; heart throbbing, swelling of eyelids, face, or lips; or a skin  
650 rash, skin lumps, or hives happens rarely. If it happens to you, then tell your doctor  
651 immediately. Do not take any more AMERGE Tablets unless your doctor tells you to do so.
- 652 • Some people may have feelings of tingling, heat, flushing (redness of face lasting a short  
653 time), heaviness or pressure after treatment with AMERGE Tablets. A few people may feel  
654 drowsy, dizzy, tired, or sick. Tell your doctor of these symptoms at your next visit.
- 655 • If you feel unwell in any other way or have any symptoms that you do not understand, you  
656 should contact your doctor immediately.

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

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

660 **7. Storing Your Medicine:**

661 Keep your medicine in a safe place where children cannot reach it. It may be harmful to  
662 children. Store your medicine away from heat and light. Do not store at temperatures above 77°F  
663 (25°C). If your medicine has expired (the expiration date is printed on the treatment pack), throw  
664 it away as instructed. If your doctor decides to stop your treatment, do not keep any leftover  
665 medicine unless your doctor tells you to. Throw away your medicine as instructed.

666  
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668 brands listed are trademarks of their respective owners and are not trademarks of  
669 GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse  
670 GlaxoSmithKline or its products.

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