

PRESCRIBING INFORMATION

1
2 **TREXIMET™**
3 **(sumatriptan and naproxen sodium)**
4 **Tablets**

5 **WARNINGS**

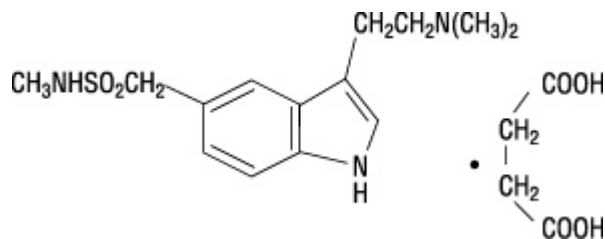
6 **Cardiovascular Risk:** TREXIMET may cause an increased risk of serious cardiovascular
7 thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may
8 increase with duration of use. Patients with cardiovascular disease or risk factors for
9 cardiovascular disease may be at greater risk (see WARNINGS: Cardiovascular Effects).

10
11 **Gastrointestinal Risk:** TREXIMET contains a nonsteroidal anti-inflammatory drug
12 (NSAID). NSAID-containing products cause an increased risk of serious gastrointestinal
13 adverse events including bleeding, ulceration, and perforation of the stomach or intestines,
14 which can be fatal. These events can occur at any time during use and without warning
15 symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see
16 **WARNINGS: Risk of Gastrointestinal Ulceration, Bleeding, and Perforation With**
17 **Nonsteroidal Anti-inflammatory Drug Therapy**).

18 **DESCRIPTION**

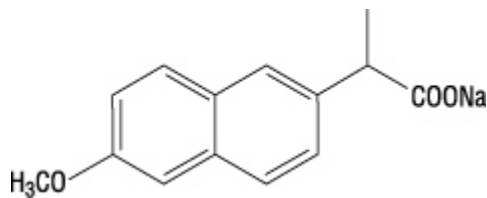
19 TREXIMET contains sumatriptan (as the succinate), a selective 5-hydroxytryptamine₁
20 (5-HT₁) receptor subtype agonist, and naproxen sodium, a member of the arylacetic acid group
21 of nonsteroidal anti-inflammatory drugs (NSAIDs).

22 Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-
23 indole-5-methanesulfonamide succinate (1:1), and it has the following structure:



27 The empirical formula is C₁₄H₂₁N₃O₂S•C₄H₆O₄, representing a molecular weight of 413.5.
28 Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in
29 saline.

30 Naproxen sodium is chemically designated as (S)-6-methoxy- α -methyl-2-naphthaleneacetic
31 acid, sodium salt, and it has the following structure:



32
33

34 The empirical formula is $C_{14}H_{13}NaO_3$, representing a molecular weight of 252.23. Naproxen
35 sodium is a white-to-creamy white crystalline solid, freely soluble in water at neutral pH.

36 Each TRIXIMET Tablet for oral administration contains 119 mg of sumatriptan succinate
37 equivalent to 85 mg of sumatriptan and 500 mg of naproxen sodium. Each tablet also contains
38 the inactive ingredients croscarmellose sodium, dextrose monohydrate, dibasic calcium
39 phosphate, FD&C Blue No. 2, lecithin, magnesium stearate, maltodextrin, microcrystalline
40 cellulose, povidone, sodium bicarbonate, sodium carboxymethylcellulose, talc, and titanium
41 dioxide.

42 CLINICAL PHARMACOLOGY

43 **Mechanism of Action:** TRIXIMET contains sumatriptan, a 5-HT₁ receptor agonist that
44 mediates vasoconstriction of the human basilar artery and vasculature of human dura mater,
45 which correlates with the relief of migraine headache. It also contains naproxen, an NSAID that
46 inhibits the synthesis of inflammatory mediators. Therefore, sumatriptan and naproxen contribute
47 to the relief of migraine through pharmacologically different mechanisms of action.

48 Sumatriptan is a 5-HT₁ receptor agonist that binds with high affinity to 5-HT_{1B} and 5-HT_{1D}
49 receptors. Sumatriptan has only a weak affinity for 5-HT_{1A}, 5-HT_{5A}, and 5-HT₇ receptors and no
50 significant affinity (as measured using standard radioligand binding assays) or pharmacological
51 activity at 5-HT₂, 5-HT₃, or 5-HT₄ receptor subtypes or at alpha₁-, alpha₂-, or beta-adrenergic;
52 dopamine₁; dopamine₂; muscarinic; or benzodiazepine receptors. In addition to causing
53 vasoconstriction, experimental data from animal studies show that sumatriptan also activates
54 5-HT₁ receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels.
55 Such an action may contribute to the antimigrainous effect of sumatriptan in humans. In the
56 anesthetized dog, sumatriptan selectively reduces carotid arterial blood flow with little or no
57 effect on arterial blood pressure or total peripheral resistance.

58 Naproxen sodium is an NSAID with analgesic and antipyretic properties. The sodium salt of
59 naproxen has been developed as a more rapidly absorbed formulation of naproxen for use as an
60 analgesic. The mechanism of action of the naproxen anion, like that of other NSAIDs, is not
61 completely understood but may be related to prostaglandin synthetase inhibition.

62 **Pharmacokinetics:** TRIXIMET is a formulation of 85 mg of sumatriptan (as sumatriptan
63 succinate) and 500 mg of naproxen sodium with a distinct pharmacokinetic profile. C_{max} for
64 sumatriptan following administration of TRIXIMET occurs at approximately 1 hour (median,
65 range 0.3 to 4.0 hours). C_{max} for naproxen following administration of TRIXIMET occurs at
66 approximately 5 hours (median, range 0.3 to 12 hours). The sumatriptan half-life is
67 approximately 2 hours (15% to 43% CV) and the naproxen half-life is approximately 19 hours

68 (13% to 15% CV). The mean C_{max} for sumatriptan when given as TREXIMET is similar to that
69 of sumatriptan when given as IMITREX Tablets 100 mg alone. The median sumatriptan T_{max} is
70 only slightly different (1 hour for TREXIMET and 1.5 hours for IMITREX). The C_{max} for
71 naproxen is approximately 36% lower, and the T_{max} occurs approximately 4 hours later from
72 TREXIMET than from ANAPROX[®] DS (naproxen sodium tablets) 550 mg. AUC values for
73 sumatriptan and for naproxen are similar for TREXIMET compared to IMITREX or ANAPROX
74 DS, respectively. In a crossover study in 16 patients, the pharmacokinetics of both components
75 administered as TREXIMET were similar during a migraine attack and during a migraine-free
76 period.

77 **Absorption and Bioavailability:** Bioavailability of sumatriptan is approximately 15%,
78 primarily due to presystemic (first-pass) metabolism and partly due to incomplete absorption.

79 Naproxen is rapidly and completely absorbed from the gastrointestinal tract with an in vivo
80 bioavailability of 95%.

81 **Food Effects:** Food had no significant effect on the bioavailability of sumatriptan or
82 naproxen administered as TREXIMET, but slightly delayed the T_{max} of sumatriptan by about
83 0.6 hour. These data indicate that TREXIMET may be administered without regard to food.

84 **Distribution:** The volume of distribution of sumatriptan is 2.4 L/kg. Plasma protein binding
85 is 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been
86 evaluated, but would be expected to be minor, given the low protein binding.

87 The volume of distribution of naproxen is 0.16 L/kg. At therapeutic levels naproxen is greater
88 than 99% albumin bound. At doses of naproxen greater than 500 mg/day, there is a less than
89 proportional increase in plasma levels due to an increase in clearance caused by saturation of
90 plasma protein binding at higher doses (average trough C_{ss} = 36.5, 49.2, and 56.4 mg/L with 500,
91 1,000, and 1,500 mg daily doses of naproxen, respectively). However, the concentration of
92 unbound naproxen continues to increase proportionally to dose.

93 **Metabolism:** Most of a radiolabeled dose of sumatriptan excreted in the urine is the major
94 metabolite indole acetic acid (IAA) or the IAA glucuronide, both of which are inactive. Three
95 percent of the dose can be recovered as unchanged sumatriptan. In vitro studies with human
96 microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO),
97 predominantly the A isoenzyme, and inhibitors of that enzyme may alter sumatriptan
98 pharmacokinetics to increase systemic exposure (see CONTRAINDICATIONS and
99 PRECAUTIONS: Drug Interactions: *Monoamine Oxidase-A Inhibitors*). No significant effect
100 was seen with an MAO-B inhibitor.

101 Naproxen is extensively metabolized to 6-0-desmethyl naproxen, and both parent and
102 metabolites do not induce metabolizing enzymes.

103 **Elimination:** Radiolabeled ¹⁴C-sumatriptan administered orally is largely renally excreted
104 (about 60%), with about 40% found in the feces. The elimination half-life of sumatriptan is
105 approximately 2 hours.

106 The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any
107 dose is excreted in the urine, primarily as naproxen (less than 1%), 6-0-desmethyl naproxen (less

108 than 1%), or their conjugates (66% to 92%). The plasma half-life of the naproxen anion in
109 humans is approximately 19 hours. The corresponding half-lives of both metabolites and
110 conjugates of naproxen are shorter than 12 hours, and their rates of excretion have been found to
111 coincide closely with the rate of naproxen disappearance from the plasma. In patients with renal
112 failure, metabolites may accumulate (see PRECAUTIONS: Renal Effects).

113 **Special Populations: Renal Impairment:** TREXIMET is not recommended for use in
114 patients with creatinine clearance less than 30 mL/min (see PRECAUTIONS: Renal Effects).
115 The effect of renal impairment on the pharmacokinetics of TREXIMET has not been studied.

116 Minimal change in clinical effect would be expected with regard to sumatriptan as it is largely
117 metabolized to an inactive substance.

118 Since naproxen and its metabolites and conjugates are primarily excreted by the kidney, the
119 potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency.
120 Elimination of naproxen is decreased in patients with severe renal impairment.

121 **Hepatic Impairment:** Because TREXIMET is a fixed-dose combination that cannot be
122 adjusted for this patient population, it is contraindicated in patients with hepatic impairment (see
123 CONTRAINDICATIONS and PRECAUTIONS: Hepatic Effects). The effect of hepatic
124 impairment on the pharmacokinetics of TREXIMET has not been studied. Sumatriptan is
125 contraindicated in patients with severe hepatic impairment and the dose is limited to 50 mg in
126 patients with liver disease.

127 **Age:** The effect of age (elderly or pediatric patients) on the pharmacokinetics of TREXIMET
128 has not been studied. Elderly patients are more likely to have decreased hepatic function and
129 decreased renal function (see PRECAUTIONS: Geriatric Use).

130 The pharmacokinetics of oral sumatriptan in the elderly (mean age, 72 years; 2 males and 4
131 females) and in patients with migraine (mean age, 38 years; 25 males and 155 females) were
132 similar to that in healthy male subjects (mean age, 30 years).

133 **Gender:** In a pooled analysis of 5 pharmacokinetic studies, there was no effect of gender on
134 the systemic exposure of TREXIMET. In a study comparing the pharmacokinetics of
135 sumatriptan in females and males, no differences were observed between genders for AUC, C_{max} ,
136 T_{max} , and $T_{1/2}$.

137 **Race:** The effect of race on the pharmacokinetics of TREXIMET has not been studied. The
138 systemic clearance and C_{max} of sumatriptan were similar in black (n = 34) and Caucasian (n = 38)
139 healthy male subjects.

140 **Drug Interactions:** No formal drug interaction studies have been conducted with TREXIMET.

141 **Monoamine Oxidase Inhibitors:** TREXIMET is contraindicated in patients taking MAO-
142 A inhibitors (see CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions). Treatment
143 with MAO-A inhibitors generally leads to an increase of sumatriptan plasma levels. This
144 interaction has not been seen with an MAO-B inhibitor.

145 **Alcohol:** The effect of alcohol consumption on the pharmacokinetics of TREXIMET has not
146 been studied. Alcohol consumed 30 minutes prior to sumatriptan ingestion had no effect on the
147 pharmacokinetics of sumatriptan.

148 **CLINICAL TRIALS**

149 The efficacy of TREXIMET in providing relief from migraine was demonstrated in 2
150 randomized, double-blind, multicenter, parallel-group trials utilizing placebo and each individual
151 active component of TREXIMET (sumatriptan and naproxen sodium) as comparison treatments.
152 Patients enrolled in these 2 trials were predominately female (87%) and Caucasian (88%), with a
153 mean age of 40 years (range 18 to 65 years). Patients were instructed to treat a migraine of
154 moderate to severe pain with 1 tablet. Patients evaluated their headache pain 2 hours after taking
155 1 dose of study medication; headache relief was defined as a reduction in headache severity from
156 moderate or severe pain to mild or no pain. Associated symptoms of nausea, photophobia, and
157 phonophobia were also evaluated. Sustained pain free was defined as a reduction in headache
158 severity from moderate or severe pain to no pain at 2 hours postdose without a return of mild,
159 moderate, or severe pain and no use of rescue medication for 24 hours postdose. The results from
160 the 2 controlled clinical trials are summarized in Table 1. In both trials, the percentage of patients
161 achieving headache pain relief 2 hours after treatment was significantly greater among patients
162 receiving TREXIMET (65% and 57%) compared with those who received placebo (28% and
163 29%).

164 Further, the percentage of patients who remained pain free without use of other medications
165 through 24 hours postdose was significantly greater among patients receiving a single dose of
166 TREXIMET (25% and 23%) compared with those who received placebo (8% and 7%) or either
167 sumatriptan (16% and 14%) or naproxen sodium (10%) alone.

168
169 **Table 1. Percentage of Patients With 2-Hour Pain Relief and Sustained Pain Free**
170 **Following Treatment***

	TREXIMET	Sumatriptan 85 mg	Naproxen Sodium 500 mg	Placebo
2-Hour Pain Relief				
Study 1 (all patients)	65% [†] n = 364	55% n = 361	44% n = 356	28% n = 360
Study 2 (all patients)	57% [†] n = 362	50% n = 362	43% n = 364	29% n = 382
Sustained Pain Free (2-24 Hours)				
Study 1	25% [‡] n = 364	16% n = 361	10% n = 356	8% n = 360
Study 2	23% [‡] n = 362	14% n = 362	10% n = 364	7% n = 382

171 * p values provided only for prespecified comparisons.

172 [†]p<0.05 versus placebo and sumatriptan.

173 [‡]p<0.01 versus placebo, sumatriptan, and naproxen sodium.

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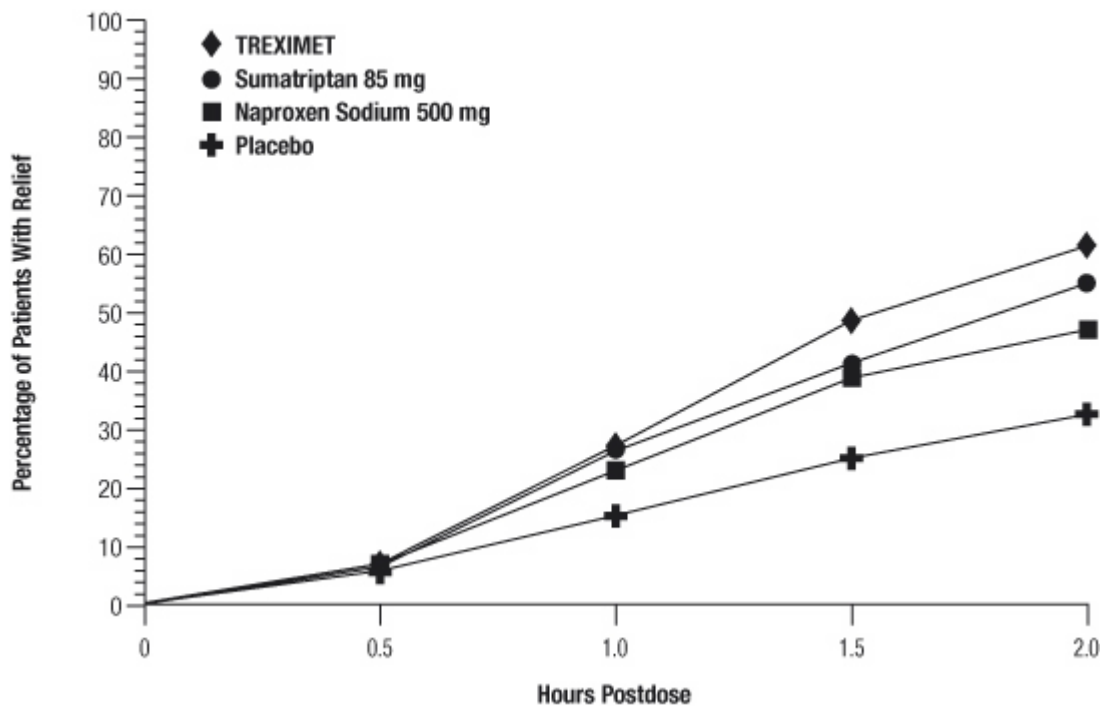
175 Note that comparisons of the performance of different drugs based upon results
176 obtained in different clinical trials are never reliable. Because studies are generally
177 conducted at different times, with different samples of patients, by different investigators,
178 employing different criteria and/or different interpretations of the same criteria, under
179 different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment
180 response and the timing of response may be expected to vary considerably from study to
181 study.

182 The percentage of patients achieving initial headache pain relief within 2 hours following
183 treatment with TREXIMET is shown in Figure 1.

184

185 **Figure 1. Percentage of Patients With Initial Headache Pain Relief Within 2 Hours**

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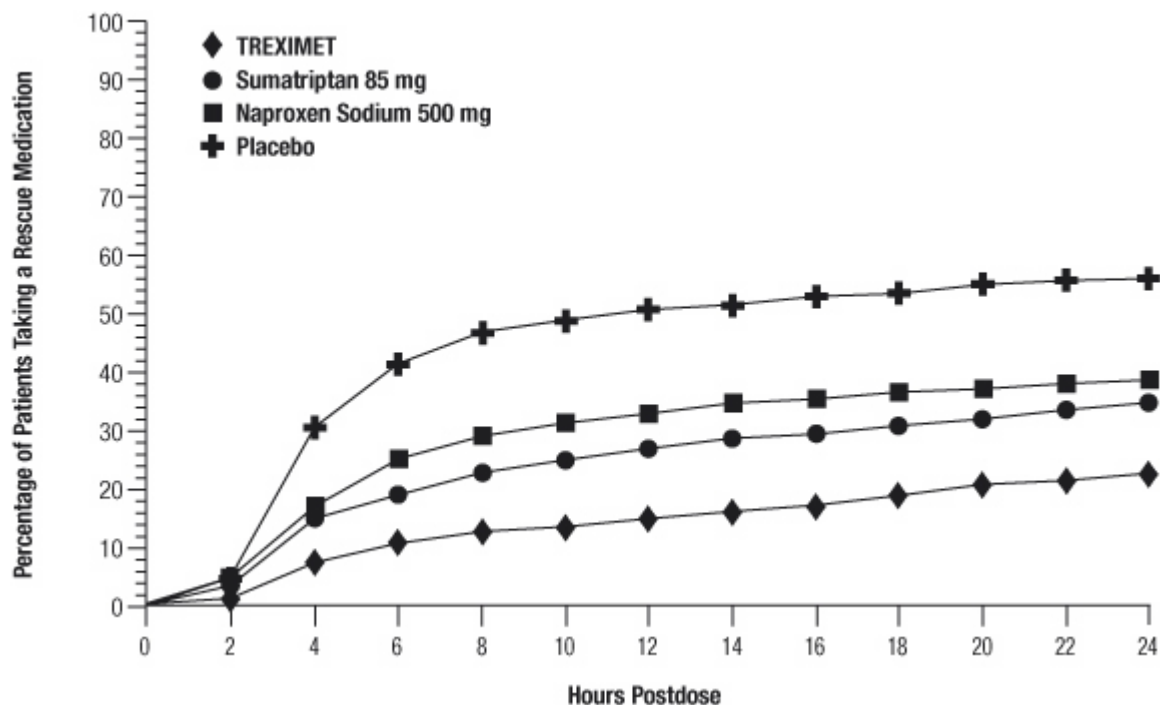
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189 Compared with placebo, there was a decreased incidence of photophobia, phonophobia, and
190 nausea 2 hours after the administration of TREXIMET. The estimated probability of taking a
191 rescue medication over the first 24 hours is shown in Figure 2.

192

193 **Figure 2. Estimated Probability of Taking a Rescue Medication Over the 24 Hours**
194 **Following the First Dose***
195



196
197 * Kaplan-Meier plot based on data obtained in the 2 clinical controlled trials providing evidence
198 of efficacy with patients not using additional treatments censored to 24 hours. Plot also
199 includes patients who had no response to the initial dose. No rescue medication was allowed
200 within 2 hours postdose.
201

202 TREXIMET was more effective than placebo regardless of the presence of aura; duration of
203 headache prior to treatment; gender, age, or weight of the patient; or concomitant use of oral
204 contraceptives or common migraine prophylactic drugs (e.g., beta-blockers, anti-epileptic drugs,
205 tricyclic antidepressants).

206 **INDICATIONS AND USAGE**

207 TREXIMET is indicated for the acute treatment of migraine attacks with or without aura in
208 adults. Carefully consider the potential benefits and risks of TREXIMET and other treatment
209 options when deciding to use TREXIMET.

210 TREXIMET is not intended for the prophylactic therapy of migraine or for use in the
211 management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and
212 effectiveness of TREXIMET have not been established for cluster headache.

213 **CONTRAINDICATIONS**

214 **Cardiac, Cerebrovascular, or Peripheral Vascular Disease: TREXIMET should not**
215 **be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular,**

216 or peripheral vascular syndromes. In addition, patients with other significant underlying
217 cardiovascular diseases should not receive TREXIMET, nor should patients who have had
218 coronary artery bypass graft (CABG) surgery. Ischemic cardiac syndromes include, but
219 are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic
220 forms of angina, such as the Prinzmetal variant), all forms of myocardial infarction, and
221 silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to,
222 strokes of any type as well as transient ischemic attacks. Peripheral vascular disease
223 includes, but is not limited to, ischemic bowel disease (see WARNINGS: Cardiovascular
224 Effects).

225 **Uncontrolled Hypertension:** TREXIMET should not be given to patients with
226 uncontrolled hypertension because the components have been shown to increase blood
227 pressure.

228 **Monoamine Oxidase-A Inhibitors:** Concurrent administration of MAO-A inhibitors or
229 use of TREXIMET within 2 weeks of discontinuation of MAO-A inhibitor therapy is
230 contraindicated (see CLINICAL PHARMACOLOGY: Drug Interactions and
231 PRECAUTIONS: Drug Interactions).

232 **Ergotamine-Containing or Ergot-Type Medications:** TREXIMET and any
233 ergotamine-containing or ergot-type medication (like dihydroergotamine or methysergide)
234 should not be used within 24 hours of each other (see PRECAUTIONS: Drug Interactions).

235 **Other 5-HT₁ Agonists:** Since TREXIMET contains sumatriptan, it should not be
236 administered within 24 hours of another 5-HT₁ agonist.

237 **Hemiplegic or Basilar Migraine:** TREXIMET should not be administered to patients
238 with hemiplegic or basilar migraine.

239 **Hepatic Impairment:** TREXIMET is contraindicated in patients with hepatic impairment
240 (see CLINICAL PHARMACOLOGY: Special Populations, PRECAUTIONS: Hepatic
241 Effects, and PRECAUTIONS: Geriatric Use).

242 **Allergy to Naproxen/Asthma, Nasal Polyps, Urticaria, and Hypotension**
243 **Associated With Nonsteroidal Anti-inflammatory Drugs:** TREXIMET is
244 contraindicated in patients who have had allergic reactions to prescription as well as to
245 over-the-counter products containing naproxen. It is also contraindicated in patients in
246 whom aspirin or other nonsteroidal anti-inflammatory/analgesic drugs induce the
247 syndrome of asthma, rhinitis, and nasal polyps. Anaphylactic/anaphylactoid reactions to
248 naproxen, whether of the true allergic type or the pharmacologic idiosyncratic type (e.g.,
249 aspirin hypersensitivity syndrome), usually but not always occur in patients with a known
250 history of such reactions. Both types of reactions have the potential of being fatal.
251 Therefore, careful questioning of patients for medical conditions such as asthma, nasal
252 polyps, urticaria, and hypotension associated with NSAIDs before starting therapy is
253 important. In addition, if such symptoms occur during therapy, treatment should be
254 discontinued (see WARNINGS: Anaphylactic/Anaphylactoid Reactions and
255 PRECAUTIONS: Preexisting Asthma).

256 **Hypersensitivity to Sumatriptan or Naproxen:** TREXIMET is contraindicated in
257 patients with hypersensitivity to sumatriptan, naproxen, or any other component of the
258 product.

259 **WARNINGS**

260 TREXIMET should only be used where a clear diagnosis of migraine headache has been
261 established.

262 **Cardiovascular Effects: Risk of Myocardial Ischemia and/or Infarction and Other**
263 **Adverse Cardiac Events:** TREXIMET should not be given to patients with documented
264 ischemic or vasospastic coronary artery disease (CAD) or to patients with a history of
265 CABG surgery (see CONTRAINDICATIONS). It is strongly recommended that
266 sumatriptan-containing products not be given to patients in whom unrecognized CAD is
267 predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker,
268 obesity, diabetes, strong family history of CAD, female with surgical or physiological
269 menopause, male over 40 years of age) unless a cardiovascular evaluation provides
270 satisfactory clinical evidence that the patient is reasonably free of CAD and ischemic
271 myocardial disease or other significant underlying cardiovascular disease. The sensitivity
272 of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to
273 coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the
274 patient's medical history or electrocardiographic investigations reveal findings indicative
275 of, or consistent with, coronary artery vasospasm or myocardial ischemia, TREXIMET
276 should not be administered (see CONTRAINDICATIONS).

277 For patients with risk factors predictive of CAD who are determined to have a
278 satisfactory cardiovascular evaluation, it is strongly recommended that administration of
279 the first dose of TREXIMET take place in the setting of a physician's office or similar
280 medically staffed and equipped facility unless the patient has previously received
281 sumatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms,
282 consideration should be given to obtaining an electrocardiogram (ECG) immediately
283 following first-time use of TREXIMET in patients with risk factors.

284 It is recommended that patients who are intermittent long-term users of TREXIMET
285 and who have or acquire risk factors predictive of CAD as described above undergo
286 periodic cardiovascular evaluation as they continue to use TREXIMET.

287 The systematic approach described above is intended to reduce the likelihood that
288 patients with unrecognized cardiovascular disease will be inadvertently exposed to
289 sumatriptan-containing products.

290 **Cardiac Events and Fatalities Associated With 5-HT₁ Agonists:** Serious adverse
291 cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac
292 rhythm, and death have been reported within a few hours following the administration of
293 sumatriptan. Considering the extent of use of 5-HT₁ agonists in patients with migraine, the
294 incidence of these events is extremely low.

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

300 **Cardiovascular Thrombotic Events and Fatalities Associated With Nonsteroidal**
301 **Anti-inflammatory Drugs:** Clinical trials of several COX-2 selective and nonselective
302 NSAIDs of up to 3 years' duration have shown an increased risk of serious cardiovascular
303 thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both
304 COX-2 selective and nonselective, may have a similar risk. Patients with known cardiovascular
305 disease or risk factors for cardiovascular disease may be at greater risk. To minimize the
306 potential risk for an adverse cardiovascular event in patients treated with an NSAID, the lowest
307 effective dose should be used for the shortest duration possible. Physicians and patients should
308 remain alert for the development of such events, even in the absence of previous cardiovascular
309 symptoms. Patients should be informed about the signs and/or symptoms of serious
310 cardiovascular events and the steps to take if they occur.

311 There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of
312 serious cardiovascular thrombotic events associated with NSAID use. The concurrent use of
313 aspirin and an NSAID does increase the risk of serious gastrointestinal events (see WARNINGS:
314 Risk of Gastrointestinal Ulceration, Bleeding, and Perforation With Nonsteroidal
315 Anti-inflammatory Drug Therapy).

316 **Premarketing Experience With TREXIMET:** Among 3,302 patients with migraine who
317 received TREXIMET in premarketing controlled and uncontrolled clinical trials, a 47-year-old
318 female with cardiac risk factors in an open-label 12-month safety study experienced signs and
319 symptoms of acute coronary syndrome approximately 2 hours after receiving TREXIMET.

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

331 **Other Vasospasm-Related Events:** Sumatriptan may cause vasospastic reactions other
332 than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with
333 abdominal pain and bloody diarrhea have been reported. Transient and permanent blindness and

334 significant partial vision loss have been reported with the use of sumatriptan. Visual disorders
335 may also be part of a migraine attack.

336 **Increase in Blood Pressure:** TREXIMET is contraindicated in patients with uncontrolled
337 hypertension (see CONTRAINDICATIONS). TREXIMET should be used with caution in
338 patients with controlled hypertension.

339 Significant elevation in blood pressure, including hypertensive crisis, has been reported in
340 patients with and without a history of hypertension receiving sumatriptan. Sumatriptan-
341 containing products should be administered with caution to patients with controlled hypertension
342 as transient increases in blood pressure and peripheral vascular resistance have been observed.

343 NSAID-containing products can lead to onset of new hypertension or worsening of
344 preexisting hypertension, either of which may contribute to the increased incidence of
345 cardiovascular events. Patients taking thiazides or loop diuretics may have impaired response to
346 these therapies when taking NSAIDs. The potential effect on blood pressure associated with
347 long-term use of TREXIMET has not been studied. Blood pressure should be monitored closely
348 during the initiation of NSAID treatment and throughout the course of therapy.

349 **Congestive Heart Failure and Edema:** TREXIMET should be used with caution in
350 patients with fluid retention or heart failure. Fluid retention and edema have been observed in
351 some patients taking NSAIDs. Since each TREXIMET tablet contains 61.2 mg of sodium (about
352 2.7 mEq/500 mg of naproxen sodium), this should be considered in patients whose overall intake
353 of sodium must be severely restricted.

354 **Serotonin Syndrome:** The development of a potentially life-threatening serotonin syndrome
355 may occur with triptans, including treatment with TREXIMET, particularly during combined use
356 with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake
357 inhibitors (SNRIs). If concomitant treatment with TREXIMET and an SSRI (e.g., fluoxetine,
358 paroxetine, sertraline, fluvoxamine, citalopram, escitalopram) or SNRI (e.g., venlafaxine,
359 duloxetine) is clinically warranted, careful observation of the patient is advised, particularly
360 during treatment initiation and dose increases. Serotonin syndrome symptoms may include
361 mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g.,
362 tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia,
363 incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) (see
364 PRECAUTIONS: Drug Interactions).

365 **Risk of Gastrointestinal Ulceration, Bleeding, and Perforation With Nonsteroidal
366 Anti-inflammatory Drug Therapy:** TREXIMET contains an NSAID. NSAID-containing
367 products can cause serious gastrointestinal adverse events including inflammation, bleeding,
368 ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal.

369 These serious adverse events can occur at any time, with or without warning symptoms, in
370 patients treated with NSAIDs. Only 1 in 5 patients who develop a serious upper gastrointestinal
371 adverse event on NSAID therapy is symptomatic. Upper gastrointestinal ulcers, gross bleeding,
372 or perforation caused by NSAIDs appear to occur in approximately 1% of patients treated daily
373 for 3 to 6 months and in about 2% to 4% of patients treated for 1 year. These trends continue

374 with longer duration of use, increasing the likelihood of developing a serious gastrointestinal
375 event at some time during the course of therapy. However, even short-term therapy is not
376 without risk. Among 3,302 patients with migraine who received TREXIMET in premarketing
377 controlled and uncontrolled clinical trials, 1 patient experienced a recurrence of gastric ulcer
378 after taking 8 doses over 3 weeks, and 1 patient developed a gastric ulcer after treating an
379 average of 8 attacks per month over 7 months.

380 NSAID-containing products, including TREXIMET, should be prescribed with extreme
381 caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a
382 prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a
383 greater than 10-fold increased risk for developing gastrointestinal bleeding compared to patients
384 with neither of these risk factors. Other factors that increase the risk for gastrointestinal bleeding
385 in patients treated with NSAIDs include concomitant use of oral corticosteroids or
386 anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor
387 general health status. Most spontaneous reports of fatal gastrointestinal events are in elderly or
388 debilitated patients, and therefore special care should be taken in treating this population.

389 To minimize the potential risk for an adverse gastrointestinal event in patients treated with an
390 NSAID-containing product, the lowest effective dose should be used for the shortest possible
391 duration. Patients and physicians should remain alert for signs and symptoms of gastrointestinal
392 ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and
393 treatment if a serious gastrointestinal adverse event is suspected. This should include
394 discontinuation of the NSAID until a serious gastrointestinal adverse event is ruled out. For
395 high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

396 **Renal Effects:** Long-term administration of NSAIDs has resulted in renal papillary necrosis
397 and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins
398 have a compensatory role in the maintenance of renal perfusion. In these patients administration
399 of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily,
400 in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk
401 of this reaction are those with impaired renal function, heart failure, liver dysfunction, those
402 taking diuretics and angiotensin-converting enzyme (ACE) inhibitors, and the elderly.
403 Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

404 **Advanced Renal Disease:** Treatment with TREXIMET is not recommended in patients
405 with advanced renal disease. If therapy with TREXIMET must be initiated, close monitoring of
406 the patient's renal function is advisable (see CLINICAL PHARMACOLOGY: Pharmacokinetics
407 and PRECAUTIONS: Renal Effects). No information is available from controlled clinical
408 studies regarding the use of TREXIMET in patients with advanced renal disease.

409 **Anaphylactic/Anaphylactoid Reactions:** As with other NSAID-containing products,
410 anaphylactic/anaphylactoid reactions may occur in patients without known prior exposure to
411 naproxen. TREXIMET should not be given to patients with the aspirin triad. This symptom
412 complex typically occurs in patients with asthma who experience rhinitis with or without nasal
413 polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other

414 NSAIDs (see CONTRAINDICATIONS, PRECAUTIONS: Preexisting Asthma, and
415 PRECAUTIONS: Drug Interactions).

416 Anaphylactic/anaphylactoid reactions have occurred in patients receiving sumatriptan. Such
417 reactions can be life-threatening or fatal. In general, anaphylactic reactions to drugs are more
418 likely to occur in individuals with a history of sensitivity to multiple allergens (see
419 CONTRAINDICATIONS). Emergency help should be sought in cases where an anaphylactoid
420 reaction occurs. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

421 **Skin Reactions:** NSAID-containing products, including TREXIMET, can cause serious
422 adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal
423 necrolysis, which can be fatal. These serious events may occur without warning. Patients should
424 be informed about the signs and symptoms of serious skin manifestations and use of the drug
425 should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

426 **Pregnancy:** TREXIMET should not be used in late pregnancy because NSAID-containing
427 products have been shown to cause premature closure of the ductus arteriosus. TREXIMET
428 should not be used during early pregnancy unless the potential benefit justifies the potential risk
429 to the fetus (see PRECAUTIONS: Pregnancy).

430 **PRECAUTIONS**

431 **Naproxen-Containing Products: TREXIMET and other naproxen-containing products**
432 **should not be used concomitantly since they all circulate in the plasma as the naproxen**
433 **anion.**

434 **Chest, Jaw, or Neck Pain/Discomfort:** Chest discomfort and jaw or neck tightness have
435 been reported following use of sumatriptan. Only rarely have these symptoms been associated
436 with ischemic ECG changes. However, because sumatriptan may cause coronary artery
437 vasospasm, patients who experience signs or symptoms suggestive of angina following
438 TREXIMET should be evaluated for the presence of CAD or a predisposition to Prinzmetal
439 variant angina before receiving additional doses of TREXIMET and should be monitored
440 electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients
441 who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic
442 bowel syndrome or Raynaud syndrome, following TREXIMET should be evaluated for
443 atherosclerosis or predisposition to vasospasm (see WARNINGS: Cardiovascular Effects).

444 **Diseases That May Alter the Absorption, Metabolism, or Excretion of Drugs:**
445 TREXIMET should also be administered with caution to patients with diseases that may alter the
446 absorption, metabolism, or excretion of drugs, such as impaired renal function.

447 **Seizures:** TREXIMET should be used with caution in patients with a history of epilepsy or
448 conditions associated with a lowered seizure threshold. There have been reports of seizure
449 following administration of sumatriptan.

450 **Other Potentially Serious Neurologic Conditions:** Care should be taken to exclude other
451 potentially serious neurologic conditions before treating headache in patients not previously
452 diagnosed with migraine headache or who experience a headache that is atypical for them. There

453 have been reports where patients received sumatriptan for severe headaches that were
454 subsequently shown to have been secondary to an evolving neurologic lesion (see WARNINGS:
455 Drug-Associated Cerebrovascular Events and Fatalities). For a given attack, if a patient does not
456 respond to the first dose of TREXIMET, the diagnosis of migraine should be reconsidered before
457 administration of a second dose.

458 **Hepatic Effects: TREXIMET is contraindicated in patients with hepatic impairment (see**
459 **CONTRAINDICATIONS and CLINICAL PHARMACOLOGY).** A patient with symptoms
460 and/or signs suggesting liver dysfunction or in whom an abnormal liver test has occurred should
461 be evaluated for evidence of the development of a more severe hepatic reaction while on therapy
462 with TREXIMET. Borderline elevations of 1 or more liver tests may occur in up to 15% of
463 patients who take NSAID-containing products. These abnormalities may progress, may remain
464 essentially unchanged, or may be transient with continued therapy. Notable (3 times the upper
465 limit of normal) elevations of SGPT (ALT) or SGOT (AST) have been reported in approximately
466 1% of patients in clinical trials with NSAIDs. In addition, cases of severe hepatic reactions,
467 including jaundice and fatal fulminant hepatitis, liver necrosis, and hepatic failure, some of them
468 with fatal outcomes, have been reported with NSAIDs. A patient with symptoms and/or signs
469 suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be
470 evaluated for evidence of the development of a more severe hepatic reaction while on therapy
471 with TREXIMET. If clinical signs and symptoms consistent with liver disease develop, or if
472 systemic manifestations occur (e.g., eosinophilia, rash), TREXIMET should be discontinued.

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

481 **Binding to Melanin-Containing Tissues:** In rats treated with a single subcutaneous dose
482 (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half-life of
483 radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or
484 its metabolites bind to the melanin of the eye. Because there could be an accumulation in
485 melanin-rich tissues over time, sumatriptan could possibly cause toxicity in these tissues after
486 extended use. However, no effects on the retina related to treatment with sumatriptan were noted
487 in any of the oral or subcutaneous toxicity studies. Although no systematic monitoring of
488 ophthalmologic function was undertaken in clinical trials and no specific recommendations for
489 ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-
490 term ophthalmologic effects.

491 **Corneal Opacities:** Sumatriptan causes corneal opacities and defects in the corneal epithelium
492 in dogs (see ANIMAL TOXICOLOGY). Adverse eye findings have also been observed in

493 animal studies with some NSAIDs. Patients were not systematically evaluated for these changes
494 in clinical trials. However, since the animal findings raise the possibility that adverse effects on
495 the eye may occur in humans, it is recommended that ophthalmic studies be carried out if any
496 change or disturbance in vision occurs.

497 **Renal Effects:** Caution is recommended in patients with preexisting kidney disease or
498 dehydration (see WARNINGS: Renal Effects). Naproxen and its metabolites are eliminated
499 primarily by the kidneys; therefore, TREXIMET should be used with caution in patients with
500 significantly impaired renal function, and monitoring of serum creatinine and/or creatinine
501 clearance is advised in these patients. TREXIMET is not recommended for use in patients with
502 creatinine clearance less than 30 mL/min (see CLINICAL PHARMACOLOGY: Special
503 Populations).

504 **Hematological Effects:** Patients on long-term treatment with NSAIDs, including
505 TREXIMET, should have their hemoglobin or hematocrit checked if they exhibit any signs or
506 symptoms of anemia. Anemia is sometimes seen in patients receiving NSAIDs. This may be due
507 to fluid retention, occult or gross gastrointestinal blood loss, or an incompletely described effect
508 upon erythropoiesis. Patients receiving TREXIMET who may be adversely affected by
509 alterations in platelet function, such as those with coagulation disorders or patients receiving
510 anticoagulants, should be carefully monitored. NSAID-containing products inhibit platelet
511 aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their
512 effect on platelet function is quantitatively less, of shorter duration, and reversible.

513 **Preexisting Asthma:** Patients with asthma may have aspirin-sensitive asthma. The use of
514 aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm
515 that can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other
516 NSAIDs has been reported in such aspirin-sensitive patients, TREXIMET should not be
517 administered to patients with this form of aspirin sensitivity and should be used with caution in
518 patients with preexisting asthma.

519 **Information for Patients:** Patients should be informed of the following information before
520 initiating therapy with TREXIMET and periodically during the course of ongoing therapy.
521 Patients should also be encouraged to read the Medication Guide that accompanies each
522 prescription dispensed.

- 523 1. TREXIMET may cause serious cardiovascular side effects such as myocardial infarction or
524 stroke, which may result in hospitalization and even death. Although serious cardiovascular
525 events can occur without warning symptoms, patients should be alert for the signs and
526 symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for
527 medical advice when observing any indicative sign or symptoms. Patients should be apprised
528 of the importance of this follow-up (see WARNINGS: Cardiovascular Effects).
- 529 2. TREXIMET, like other NSAID-containing products, may cause gastrointestinal discomfort
530 and, rarely, serious gastrointestinal side effects such as ulcers and bleeding, which may result
531 in hospitalization and even death. Although serious gastrointestinal tract ulcerations and
532 bleeding can occur without warning symptoms, patients should be alert for the signs and

- 533 symptoms of ulcerations and bleeding and should ask for medical advice when observing any
534 indicative sign or symptoms, including epigastric pain, dyspepsia, melena, and hematemesis.
535 Patients should be apprised of the importance of this follow-up (see WARNINGS: Risk of
536 Gastrointestinal Ulceration, Bleeding, and Perforation With Nonsteroidal Anti-inflammatory
537 Drug Therapy).
- 538 3. TREXIMET, like other NSAID-containing products, may increase the risk of serious skin side
539 effects such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal
540 necrolysis, which may result in hospitalizations and even death. Although serious skin
541 reactions may occur without warning, patients should be alert for the signs and symptoms of
542 skin rash and blisters, fever, or other signs of hypersensitivity such as itching and should ask
543 for medical advice when observing any indicative signs or symptoms. Patients should be
544 advised to stop the drug immediately if they develop any type of rash and contact their
545 physicians as soon as possible.
- 546 4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to
547 their physicians.
- 548 5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g.,
549 nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, flu-like
550 symptoms). If these occur, patients should be instructed to stop therapy and seek immediate
551 medical therapy.
- 552 6. Patients should be informed of the signs of an anaphylactic/anaphylactoid reaction (e.g.,
553 difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed
554 to seek immediate emergency help (see WARNINGS: Anaphylactic/Anaphylactoid
555 Reactions).
- 556 7. TREXIMET should not be used in late pregnancy because NSAID-containing products have
557 been shown to cause premature closure of the ductus arteriosus. TREXIMET should not be
558 used during early pregnancy unless the potential benefit justifies the potential risk to the fetus.
- 559 8. Patients should be cautioned about the risk of serotonin syndrome, particularly during
560 concomitant use with SSRIs or SNRIs.
- 561 9. Caution should be exercised by patients whose activities require alertness if they experience
562 drowsiness, dizziness, vertigo, or depression during therapy with TREXIMET.
- 563 **Laboratory Tests:** Because serious gastrointestinal tract ulcerations and bleeding can occur
564 without warning symptoms, physicians should monitor for signs or symptoms of gastrointestinal
565 bleeding. If clinical signs and symptoms consistent with liver or renal disease develop, systemic
566 manifestations occur (e.g., eosinophilia, rash), or abnormal liver tests persist or worsen,
567 TREXIMET should be discontinued.
- 568 **Drug Interactions: *Monoamine Oxidase-A Inhibitors:*** The use of TREXIMET in patients
569 receiving MAO-A inhibitors is contraindicated (see CLINICAL PHARMACOLOGY: Drug
570 Interactions and CONTRAINDICATIONS). MAO-A inhibitors reduce sumatriptan clearance,
571 significantly increasing systemic exposure. In patients taking MAO-A inhibitors, sumatriptan

572 plasma levels attained after treatment with recommended doses are 7-fold higher following oral
573 administration than those obtained under other conditions.

574 **Ergot-Containing Drugs:** Ergot-containing drugs have been reported to cause prolonged
575 vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use
576 of ergotamine-containing or ergot-type medications (e.g., dihydroergotamine, methysergide) and
577 TREXIMET within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

578 **Methotrexate:** Caution should be used if TREXIMET is administered concomitantly with
579 methotrexate. Naproxen sodium and other NSAIDs have been reported to reduce the tubular
580 secretion of methotrexate in an animal model, possibly increasing the toxicity of methotrexate.
581 Concomitant administration of some NSAIDs with high-dose methotrexate therapy has been
582 reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe
583 hematologic and gastrointestinal toxicity.

584 **Aspirin:** When naproxen is administered with aspirin, its protein binding is reduced,
585 although the clearance of free naproxen is not altered. The clinical significance of this interaction
586 is not known; however, as with other NSAID-containing products, concomitant administration of
587 TREXIMET and aspirin is not generally recommended because of the potential of increased
588 adverse effects.

589 **Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake**
590 **Inhibitors and Serotonin Syndrome:** Cases of life-threatening serotonin syndrome have
591 been reported during combined use of SSRIs or SNRIs and triptans (see WARNINGS: Serotonin
592 Syndrome).

593 **Angiotensin-Converting Enzyme Inhibitors:** Reports suggest that NSAIDs may
594 diminish the antihypertensive effect of ACE inhibitors. The use of TREXIMET in patients who
595 are receiving ACE inhibitors may potentiate renal disease states (see WARNINGS: Renal
596 Effects).

597 **Furosemide:** Clinical studies, as well as postmarketing observations, have shown that
598 NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This
599 response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant
600 therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see
601 WARNINGS: Renal Effects), as well as to assure diuretic efficacy.

602 **Lithium:** NSAIDs have produced an elevation of plasma lithium levels and a reduction in
603 renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal
604 clearance was decreased by approximately 20%. These effects have been attributed to inhibition
605 of renal prostaglandin synthesis by the NSAID. Thus, when TREXIMET and lithium are
606 administered concurrently, patients should be observed carefully for signs of lithium toxicity.

607 **Probenecid:** Probenecid given concurrently increases naproxen anion plasma levels and
608 extends its plasma half-life significantly.

609 **Propranolol and Other Beta-Blockers:** Propranolol 80 mg given twice daily had no
610 significant effect on sumatriptan pharmacokinetics. Naproxen and other NSAIDs can reduce the
611 antihypertensive effect of propranolol and other beta-blockers.

612 **Warfarin:** The effects of warfarin and NSAIDs on gastrointestinal bleeding are synergistic,
613 such that patients taking both drugs have a higher risk of serious gastrointestinal bleeding than
614 patients taking either drug alone.

615 **Drug/Laboratory Test Interactions:** The ability of TREXIMET to interfere with commonly
616 employed clinical laboratory tests has not been investigated.

617 Sumatriptan is not known to interfere with commonly employed clinical laboratory tests.
618 Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be
619 kept in mind when bleeding times are determined.

620 The administration of naproxen sodium may result in increased urinary values for 17-
621 ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-
622 nitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-
623 Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be
624 temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber
625 test is to be used.

626 Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

627 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** The
628 carcinogenic potential of TREXIMET has not been studied.

629 The carcinogenic potential of sumatriptan was evaluated in oral carcinogenicity studies in
630 mice (78 weeks) and rats (104 weeks). The highest dose administered to mice and rats
631 (160 mg/kg/day) is approximately 9 and 18 times, respectively, the recommended human oral
632 daily dose of 85 mg sumatriptan on a mg/m² basis. There was no evidence of an increase in
633 tumors in either species related to sumatriptan administration.

634 The carcinogenic potential of naproxen sodium was evaluated in a 2-year oral carcinogenicity
635 study in rats at doses of 8, 16, and 24 mg/kg/day and in another 2-year oral carcinogenicity study
636 in rats at a dose of 8 mg/kg/day. No evidence of tumorigenicity was found in either study, at
637 doses up to approximately 0.5 times the recommended human oral daily dose of 500 mg/day
638 naproxen sodium on a mg/m² basis.

639 **Mutagenesis:** Sumatriptan and naproxen sodium tested alone and in combination were
640 negative in an in vitro bacterial reverse mutation assay, and in an in vivo micronucleus assay in
641 mice.

642 The combination of sumatriptan and naproxen sodium was negative in an in vitro mouse
643 lymphoma tk assay in the presence and absence of metabolic activation. However, in separate in
644 vitro mouse lymphoma tk assays, naproxen sodium alone was reproducibly positive in the
645 presence of metabolic activation.

646 Naproxen sodium alone and in combination with sumatriptan was positive in an in vitro
647 clastogenicity assay in mammalian cells in the presence and absence of metabolic activation. The
648 clastogenic effect for the combination was reproducible within this assay and was greater than
649 observed with naproxen sodium alone. Sumatriptan alone was negative in these assays.

650 Chromosomal aberrations were not induced in peripheral blood lymphocytes following 7 days
651 of twice-daily dosing with TREXIMET in human volunteers.

652 In previous studies, sumatriptan alone was not mutagenic in 2 gene mutation assays (the Ames
653 test and the in vitro Chinese Hamster V79/HGPRT assay) and was not clastogenic in 2
654 cytogenetics assays (the in vitro human lymphocyte assay and the in vivo rat micronucleus
655 assay).

656 **Impairment of Fertility:** The effect of TREXIMET on fertility in animals has not been
657 studied.

658 In a study in which male and female rats were dosed daily with oral sumatriptan prior to and
659 throughout the mating period, there was a treatment-related decrease in fertility secondary to a
660 decrease in mating in animals treated with 50 and 500 mg/kg/day. The highest no-effect dose for
661 this finding was 5 mg/kg/day, or approximately 0.5 times the recommended human oral daily
662 dose of 85 mg sumatriptan on a mg/m² basis. It is not clear whether the problem is associated
663 with treatment of the males or females or both combined. In a similar study of sumatriptan by the
664 subcutaneous route there was no evidence of impaired fertility at doses up to 60 mg/kg/day.

665 **Pregnancy:** Pregnancy Category C. In developmental toxicity studies in rabbits, oral treatment
666 with sumatriptan combined with naproxen sodium (5/9, 25/45, or 50/90 mg/kg/day
667 sumatriptan/naproxen sodium) or each drug alone (50/0 or 0/90 mg/kg/day sumatriptan/naproxen
668 sodium) resulted in decreased fetal body weight in all treated groups and in increased
669 embryofetal death at the highest dose of naproxen, alone and in combination with sumatriptan.
670 Naproxen sodium, alone and in combination with sumatriptan, increased the total incidences of
671 fetal abnormalities at all doses and increased the incidences of specific malformations (cardiac
672 interventricular septal defect in the 50/90-mg/kg/day group, fused caudal vertebrae in the 50/0-
673 and 0/90-mg/kg/day groups) and variations (absent intermediate lobe of the lung, irregular
674 ossification of the skull, incompletely ossified sternal centra) in the 50/0- and 0/90-mg/kg/day
675 groups. A no-effect dose for development toxicity in rabbits was not established. The lowest
676 effect dose was 5/9 mg/kg/day sumatriptan/naproxen sodium, which was associated with plasma
677 exposures (AUC) to sumatriptan and naproxen that were 1.4 and 0.14 times, respectively, those
678 attained at the maximum recommended human oral daily dose of 85 mg sumatriptan and 500 mg
679 naproxen sodium.

680 In previous developmental toxicity studies in rats and rabbits, oral treatment with sumatriptan
681 was associated with embryoletality, fetal abnormalities, and pup mortality. Oral treatment of
682 pregnant rats with sumatriptan during the period of organogenesis resulted in an increased
683 incidence of fetal blood vessel (cervicothoracic and umbilical) abnormalities and decreased pup
684 survival at doses of 250 mg/kg/day or higher. The highest no-effect dose was approximately
685 60 mg/kg/day, which is approximately 7 times the recommended human oral daily dose of 85 mg
686 sumatriptan on a mg/m² basis. Oral treatment of pregnant rabbits with sumatriptan during the
687 period of organogenesis resulted in an increased incidence of cervicothoracic vascular and
688 skeletal abnormalities at a dose of 50 mg/kg/day and embryoletality at 100 mg/kg/day. The
689 highest no-effect dose for embryotoxicity in rabbits was 15 mg/kg/day, or approximately 3 times
690 the recommended human oral daily dose of 85 mg sumatriptan on a mg/m² basis.

691 Inhibitors of prostaglandin synthesis (including naproxen) are known to delay parturition.
692 Because of this and the known effects of drugs of this class on the human fetal cardiovascular
693 system (closure of the ductus arteriosus), use during third trimester should be avoided.

694 There are no adequate and well-controlled studies in pregnant women.

695 TREXIMET should not be used during pregnancy unless the potential benefit justifies the
696 potential risk to the fetus.

697 **Pregnancy Registry:** To monitor fetal outcomes of pregnant women exposed to
698 TREXIMET, GlaxoSmithKline maintains a TREXIMET Pregnancy Registry. Physicians are
699 encouraged to register patients as soon as possible after they become pregnant and (if possible)
700 before the outcome of the pregnancy is known by calling (800) 336-2176.

701 **Labor and Delivery:** In rat studies with NSAIDs, as with other drugs known to inhibit
702 prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased
703 pup survival occurred. Naproxen-containing products are not recommended in labor and delivery
704 because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect
705 fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage.

706 **Nursing Mothers:** Both active components of TREXIMET, sumatriptan and naproxen sodium,
707 have been reported to be excreted in human breast milk. Because of the possible adverse effects
708 of these drugs on neonates, use of TREXIMET in nursing mothers should be avoided.

709 **Pediatric Use:** Safety and effectiveness of TREXIMET in pediatric patients have not been
710 established.

711 **Geriatric Use:** TREXIMET is contraindicated for use in elderly patients who have abnormal
712 hepatic function, and is not recommended for use in elderly patients who have decreased renal
713 function, higher risk for unrecognized CAD, and increases in blood pressure that may be more
714 pronounced in the elderly (see CONTRAINDICATIONS: Hepatic Impairment, WARNINGS:
715 Cardiovascular Effects, and CLINICAL PHARMACOLOGY: Pharmacokinetics).

716 **ADVERSE REACTIONS**

717 The adverse reactions reported below are specific to the clinical trials with TREXIMET. See
718 also the full prescribing information for naproxen and sumatriptan products.

719 **Incidence in Controlled Clinical Trials:** Table 2 lists adverse events that occurred in 2
720 placebo-controlled clinical trials evaluating patients who took at least 1 dose of study drug. Only
721 events that occurred at a frequency of 2% or more with TREXIMET and were more frequent
722 than in the placebo group are included in Table 2. The events cited reflect experience gained
723 under closely monitored conditions of clinical trials in a highly selected patient population. In
724 actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the
725 conditions of use, reporting behavior, and the kinds of patients treated may differ.
726

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

Adverse Event	Percent of Patients Reporting			
	TREXIMET (n = 737)	Placebo (n = 752)	Sumatriptan 85 mg (n = 735)	Naproxen Sodium 500 mg (n = 732)
Nervous system disorders				
Dizziness	4	2	2	2
Somnolence	3	2	2	2
Paresthesia	2	<1	2	<1
Gastrointestinal disorders				
Nausea	3	1	3	<1
Dyspepsia	2	1	2	1
Dry mouth	2	1	2	<1
Pain and other pressure sensations				
Chest discomfort/chest pain	3	<1	2	1
Neck/throat/jaw pain/tightness/pressure	3	1	3	1

729 * Events that occurred at a frequency of 2% or more in the group treated with TREXIMET
730 and that occurred more frequently in the group treated with TREXIMET than in the
731 placebo group.

732

733 Other events that occurred in more than 1% of patients receiving TREXIMET and occurred at
734 a frequency greater than the placebo group included asthenia, feeling hot, muscle tightness, and
735 palpitations.

736 TREXIMET was generally well tolerated. Most adverse reactions were mild and transient.
737 The incidence of adverse events in controlled clinical trials was not affected by gender or age of
738 the patients. There were insufficient data to assess the impact of race on the incidence of adverse
739 events.

740 **Other Events Observed in Migraine Clinical Trials Associated With the**
741 **Administration of TREXIMET:** The occurrence of less commonly reported adverse clinical
742 events is presented in this section. Because the reports include events observed in an open-label,
743 long-term safety study in which TREXIMET was used as needed for up to 12 months, the role of
744 TREXIMET cannot be reliably determined. Furthermore, variability associated with adverse
745 event reporting, the terminology used to describe adverse events, etc., limit the value of
746 quantitative frequency estimates provided. Event frequencies are calculated as the number of
747 patients who used TREXIMET and reported an event divided by the total number of patients
748 (N = 3,302) exposed to TREXIMET. Events listed in the previous table and text are not included

749 below. Those events described too generally to be informative or those unlikely to be associated
750 with the use of TREXIMET are excluded. Events are further classified within body system
751 categories and enumerated in order of decreasing frequency using the following definitions:
752 frequent adverse events are those occurring in at least 1/100 patients, infrequent adverse events
753 are those occurring in 1/100 to 1/1,000 patients, and rare adverse events are those occurring in
754 fewer than 1/1,000 patients.

755 **Blood and Lymphatic Disorders:** Infrequent was lymphadenopathy. Rare were anemia,
756 ecchymosis, leukopenia.

757 **Cardiac Disorders:** Infrequent was tachycardia. Rare were acute coronary syndrome,
758 cardiac flutter, congestive cardiac failure, right ventricular failure, ventricular extrasystoles.

759 **Ear and Labyrinth Disorders:** Infrequent were ear pain, tinnitus. Rare were motion
760 sickness, vertigo.

761 **Endocrine, Metabolic, and Nutrition Disorders:** Rare were diabetes mellitus, goiter,
762 hypoglycemia, hypothyroidism.

763 **Eye Disorders:** Infrequent was conjunctivitis. Rare were cataract, conjunctival hemorrhage,
764 visual disturbance.

765 **Gastrointestinal Disorders:** Frequent was abdominal pain. Infrequent were abdominal
766 distention, constipation, diarrhea, dysgeusia, dysphagia, flatulence, gastritis, gastroesophageal
767 reflux disease, vomiting. Rare were colitis, diverticulitis, gastric ulcer, irritable bowel syndrome,
768 oral mucosal blistering, swollen tongue.

769 **General Disorders:** Frequent was fatigue. Infrequent were feeling jittery, lethargy, malaise,
770 peripheral edema, pyrexia, temperature intolerance, thirst. Rare was difficulty in walking.

771 **Hepatobiliary Disorders:** Rare was biliary colic.

772 **Infections and Infestations:** Rare were kidney infection, pneumonia, sepsis,
773 staphylococcal infection, viral myocarditis.

774 **Musculoskeletal and Connective Tissue:** Infrequent were arthralgia, back pain,
775 muscular weakness, myalgia, sensation of heaviness.

776 **Nervous System Disorders:** Infrequent were burning sensation, disturbance of attention,
777 insomnia, mental impairment, tremor. Rare were aphasia, facial palsy, impairment of
778 psychomotor skills, sedation.

779 **Psychiatric Disorders:** Infrequent were anxiety, depression, irritability, nervousness. Rare
780 were disorientation, panic attack.

781 **Renal and Urinary Disorders:** Infrequent was nephrolithiasis. Rare was renal
782 insufficiency.

783 **Respiratory, Thoracic, and Mediastinal:** Infrequent were asthma, cough, dyspnea,
784 oropharyngeal swelling. Rare was pleurisy.

785 **Skin and Subcutaneous Disorders:** Infrequent were facial swelling, hyperhidrosis,
786 pruritus, rash, urticaria. Rare was systemic lupus erythematosus.

787 **Vascular Disorders:** Infrequent were flushing, hot flush, hypertension. Rare were epistaxis,
788 peripheral coldness.

789 **DRUG ABUSE AND DEPENDENCE**

790 The potential for abuse with TREXIMET has not been studied.

791 One clinical study with sumatriptan succinate injection enrolling 12 patients with a history of
792 substance abuse failed to induce subjective behavior and/or physiologic response ordinarily
793 associated with drugs that have an established potential for abuse.

794 **OVERDOSAGE**

795 Because strategies for the management of overdose are continually evolving, it is advisable to
796 contact a Poison Control Center to determine the latest recommendations for the management of
797 an overdose of any drug.

798 There have been no reports of overdosage with TREXIMET. Since sumatriptan and naproxen
799 have pharmacologically different actions, it is difficult to predict how an individual will respond
800 to an overdosage with TREXIMET.

801 Patients (N = 670) have received single oral doses of 140 to 300 mg of sumatriptan without
802 significant adverse effects. Volunteers (N = 174) have received single oral doses of 140 to
803 400 mg without serious adverse events. Overdose of sumatriptan in animals has been fatal and
804 has been heralded by convulsions, tremor, paralysis, inactivity, ptosis, erythema of the
805 extremities, abnormal respiration, cyanosis, ataxia, mydriasis, salivation, and lacrimation.

806 Significant naproxen overdosage may be characterized by lethargy, dizziness, drowsiness,
807 epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, transient alterations in
808 liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea,
809 disorientation, or vomiting. Gastrointestinal bleeding can occur. Hypertension, acute renal
810 failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have
811 been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.
812 Because naproxen sodium may be rapidly absorbed, high and early blood levels should be
813 anticipated. A few patients have experienced seizures, but it is not clear whether or not these
814 were drug related. It is not known what dose of the drug would be life threatening.

815 In animals 0.5 g/kg of activated charcoal was effective in reducing plasma levels of naproxen.
816 Patients should be managed by symptomatic and supportive care. There are no specific antidotes.
817 Hemodialysis does not decrease the plasma concentration of naproxen because of the high
818 degree of its protein binding. It is unknown what effect hemodialysis or peritoneal dialysis has
819 on the serum concentrations of sumatriptan. Emesis and/or activated charcoal (60 to 100 g in
820 adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within
821 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalization
822 of urine, or hemoperfusion may not be useful due to high protein binding.

823 **DOSAGE AND ADMINISTRATION**

824 TREXIMET is a fixed combination containing doses of sumatriptan (85 mg) and naproxen
825 sodium (500 mg) within the approved dosage ranges of the individual components (25 to 100 mg
826 of sumatriptan and 220 to 825 mg of naproxen sodium). TREXIMET contains a dose of
827 sumatriptan higher than the lowest effective dose. Individuals may vary in response to doses of

828 sumatriptan. The choice of the dose of sumatriptan, and of the use of a fixed combination such as
829 in TREXIMET should therefore be made on an individual basis, weighing the possible benefit of
830 a higher dose of sumatriptan with the potential for a greater risk of adverse events. Carefully
831 consider the potential benefits and risks of TREXIMET and other treatment options when
832 deciding to use TREXIMET.

833 The recommended dose is 1 tablet. In controlled clinical trials, single doses of TREXIMET
834 were effective for the acute treatment of migraine in adults (see CLINICAL TRIALS).

835 The efficacy of taking a second dose has not been established. Do not take more than 2
836 TREXIMET tablets in 24 hours. Dosing of tablets should be at least 2 hours apart. The safety of
837 treating an average of more than 5 migraine headaches in a 30-day period has not been
838 established.

839 TREXIMET may be administered with or without food. Tablets should not be split, crushed,
840 or chewed.

841 The combined use of TREXIMET with MAO-A inhibitors or use of TREXIMET within
842 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated (see
843 CONTRAINDICATIONS, CLINICAL PHARMACOLOGY: Drug Interactions,
844 PRECAUTIONS: Drug Interactions).

845 TREXIMET and any ergotamine-containing or ergot-type medication (like dihydroergotamine
846 or methysergide) should not be used within 24 hours of each other. TREXIMET and other 5-HT₁
847 agonists should not be administered within 24 hours of each other (see CONTRAINDICATIONS
848 and PRECAUTIONS: Drug Interactions).

849 TREXIMET is contraindicated in patients with hepatic impairment (see
850 CONTRAINDICATIONS and CLINICAL PHARMACOLOGY: Special Populations).

851 TREXIMET is not recommended for use in patients with creatinine clearance less
852 than 30 mL/min (see CLINICAL PHARMACOLOGY: Special Populations and
853 PRECAUTIONS: Renal Effects).

854 **HOW SUPPLIED**

855 TREXIMET contains 119 mg of sumatriptan succinate equivalent to 85 mg of sumatriptan
856 and 500 mg of naproxen sodium and is supplied as blue film-coated tablets debossed on one side
857 with GS YYG in compact containers of 9 tablets with a specially formulated, non-removable
858 desiccant (NDC 0173-0750-00).

859 **Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled**
860 **Room Temperature]. Do not repackage; dispense and store in original container.**

861 **ANIMAL TOXICOLOGY**

862 **Corneal Opacities:** Dogs receiving oral sumatriptan developed corneal opacities and defects
863 in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day,
864 and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a
865 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses
866 were not established; the lowest dose tested is approximately 0.8 times the recommended human

867 oral daily dose of 85 mg sumatriptan on a mg/m² basis. There was evidence of alterations in
868 corneal appearance on the first day of intranasal dosing to dogs at all doses tested.
869 TREXIMET is a trademark of GlaxoSmithKline. IMITREX, PARNATE, and PAXIL are
870 registered trademarks of GlaxoSmithKline.
871 The other brands listed are trademarks of their respective owners and are not trademarks of
872 GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse
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