

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-926

LABELING

PRESCRIBING INFORMATION

TREXIMET™
(sumatriptan and naproxen sodium)
Tablets

WARNINGS

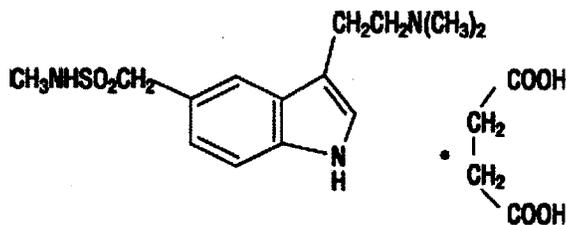
Cardiovascular Risk: TREXIMET may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater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

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

DESCRIPTION

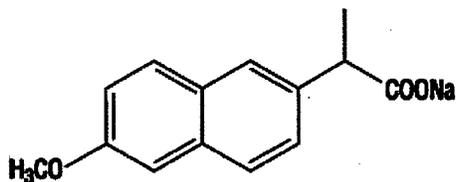
TREXIMET contains sumatriptan (as the succinate), a selective 5-hydroxytryptamine₁ (5-HT₁) receptor subtype agonist, and naproxen sodium, a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs).

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



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

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



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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 0.3-4.0 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 to those who received placebo (28% and 29%).

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

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

170 * p values provided only for prespecified comparisons.

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

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

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174 **Note that comparisons of the performance of different drugs based upon results**
 175 **obtained in different clinical trials are never reliable. Because studies are generally**

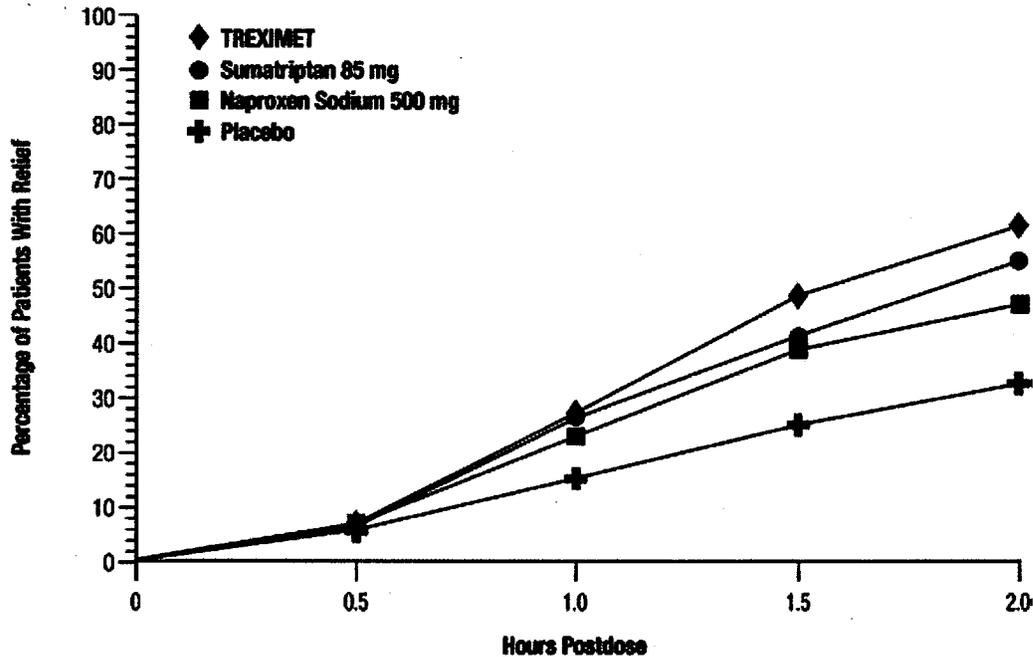
176 conducted at different times, with different samples of patients, by different investigators,
177 employing different criteria and/or different interpretations of the same criteria, under
178 different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment
179 response and the timing of response may be expected to vary considerably from study to
180 study.

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

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

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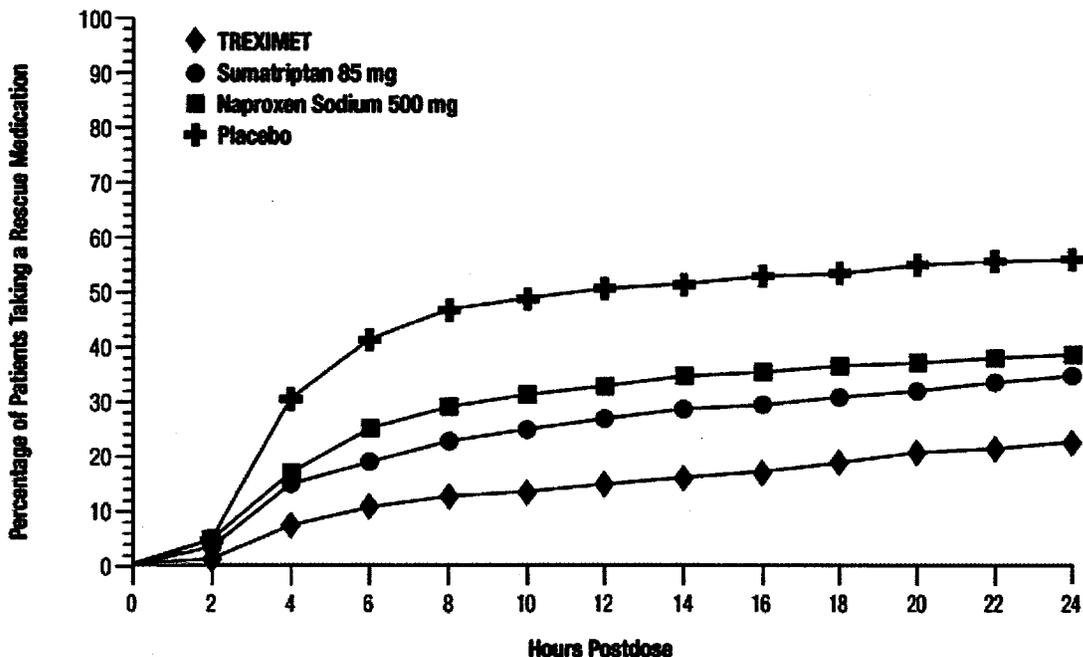
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188 Compared with placebo, there was a decreased incidence of photophobia, phonophobia, and
189 nausea 2 hours after the administration of TREXIMET. The estimated probability of taking a
190 rescue medication over the first 24 hours is shown in Figure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

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

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

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

205 **INDICATIONS AND USAGE**

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

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

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212 **CONTRAINDICATIONS**

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

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

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

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

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

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

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

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

241 **Allergy to Naproxen/Asthma, Nasal Polyps, Urticaria, and Hypotension**

242 **Associated With Nonsteroidal Anti-inflammatory Drugs:** TREXIMET is
243 contraindicated in patients who have had allergic reactions to prescription as well as to
244 over-the-counter products containing naproxen. It is also contraindicated in patients in
245 whom aspirin or other nonsteroidal anti-inflammatory/analgesic drugs induce the
246 syndrome of asthma, rhinitis, and nasal polyps. Anaphylactic/anaphylactoid reactions to
247 naproxen, whether of the true allergic type or the pharmacologic idiosyncratic type (e.g.,
248 aspirin hypersensitivity syndrome), usually but not always occur in patients with a known
249 history of such reactions. Both types of reactions have the potential of being fatal.

250 Therefore, careful questioning of patients for medical conditions such as asthma, nasal
251 polyps, urticaria, and hypotension associated with NSAIDs before starting therapy is
252 important. In addition, if such symptoms occur during therapy, treatment should be
253 discontinued (see WARNINGS: Anaphylactic/Anaphylactoid Reactions and
254 PRECAUTIONS: Preexisting Asthma).

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

258 **WARNINGS**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

429 **PRECAUTIONS**

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

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

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

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

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

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

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

472 **Binding to Melanin-Containing Tissues:** In rats treated with a single subcutaneous dose
473 (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half-life of
474 radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or
475 its metabolites bind to the melanin of the eye. Because there could be an accumulation in
476 melanin-rich tissues over time, sumatriptan could possibly cause toxicity in these tissues after
477 extended use. However, no effects on the retina related to treatment with sumatriptan were noted
478 in any of the oral or subcutaneous toxicity studies. Although no systematic monitoring of
479 ophthalmologic function was undertaken in clinical trials and no specific recommendations for
480 ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-
481 term ophthalmologic effects.

482 **Corneal Opacities:** Sumatriptan causes corneal opacities and defects in the corneal epithelium
483 in dogs (see ANIMAL TOXICOLOGY). Adverse eye findings have also been observed in
484 animal studies with some NSAIDs. Patients were not systematically evaluated for these changes
485 in clinical trials. However, since the animal findings raise the possibility that adverse effects on
486 the eye may occur in humans, it is recommended that ophthalmic studies be carried out if any
487 change or disturbance in vision occurs.

488 **Renal Effects:** Caution is recommended in patients with preexisting kidney disease or
489 dehydration (see WARNINGS: Renal Effects). Naproxen and its metabolites are eliminated
490 primarily by the kidneys; therefore, TREXIMET should be used with caution in patients with
491 significantly impaired renal function, and monitoring of serum creatinine and/or creatinine

492 clearance is advised in these patients. TREXIMET is not recommended for use in patients with
493 creatinine clearance less than 30 mL/min (see CLINICAL PHARMACOLOGY: Special
494 Populations).

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

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

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

- 514 1. TREXIMET may cause serious cardiovascular side effects such as myocardial infarction or
515 stroke, which may result in hospitalization and even death. Although serious cardiovascular
516 events can occur without warning symptoms, patients should be alert for the signs and
517 symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for
518 medical advice when observing any indicative sign or symptoms. Patients should be apprised
519 of the importance of this follow-up (see WARNINGS: Cardiovascular Effects).
- 520 2. TREXIMET, like other NSAID-containing products, may cause gastrointestinal discomfort
521 and, rarely, serious gastrointestinal side effects such as ulcers and bleeding, which may result
522 in hospitalization and even death. Although serious gastrointestinal tract ulcerations and
523 bleeding can occur without warning symptoms, patients should be alert for the signs and
524 symptoms of ulcerations and bleeding and should ask for medical advice when observing any
525 indicative sign or symptoms, including epigastric pain, dyspepsia, melena, and hematemesis.
526 Patients should be apprised of the importance of this follow-up (see WARNINGS: Risk of
527 Gastrointestinal Ulceration, Bleeding, and Perforation With Nonsteroidal Anti-inflammatory
528 Drug Therapy).
- 529 3. TREXIMET, like other NSAID-containing products, may increase the risk of serious skin side
530 effects such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal
531 necrolysis, which may result in hospitalizations and even death. Although serious skin

- 532 reactions may occur without warning, patients should be alert for the signs and symptoms of
533 skin rash and blisters, fever, or other signs of hypersensitivity such as itching and should ask
534 for medical advice when observing any indicative signs or symptoms. Patients should be
535 advised to stop the drug immediately if they develop any type of rash and contact their
536 physicians as soon as possible.
- 537 4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to
538 their physicians.
- 539 5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g.,
540 nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, flu-like
541 symptoms). If these occur, patients should be instructed to stop therapy and seek immediate
542 medical therapy.
- 543 6. Patients should be informed of the signs of an anaphylactic/anaphylactoid reaction (e.g.,
544 difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed
545 to seek immediate emergency help (see WARNINGS: Anaphylactic/Anaphylactoid
546 Reactions).
- 547 7. TREXIMET should not be used in late pregnancy because NSAID-containing products have
548 been shown to cause premature closure of the ductus arteriosus. TREXIMET should not be
549 used during early pregnancy unless the potential benefit justifies the potential risk to the fetus.
- 550 8. Patients should be cautioned about the risk of serotonin syndrome, particularly during
551 concomitant use with SSRIs or SNRIs.
- 552 9. Caution should be exercised by patients whose activities require alertness if they experience
553 drowsiness, dizziness, vertigo, or depression during therapy with TREXIMET.
- 554 **Laboratory Tests:** Because serious gastrointestinal tract ulcerations and bleeding can occur
555 without warning symptoms, physicians should monitor for signs or symptoms of gastrointestinal
556 bleeding. If clinical signs and symptoms consistent with liver or renal disease develop, systemic
557 manifestations occur (e.g., eosinophilia, rash), or abnormal liver tests persist or worsen,
558 TREXIMET should be discontinued.
- 559 **Drug Interactions: Monoamine Oxidase-A Inhibitors:** The use of TREXIMET in patients
560 receiving MAO-A inhibitors is contraindicated (see CLINICAL PHARMACOLOGY: Drug
561 Interactions and CONTRAINDICATIONS). MAO-A inhibitors reduce sumatriptan clearance,
562 significantly increasing systemic exposure. In patients taking MAO-A inhibitors, sumatriptan
563 plasma levels attained after treatment with recommended doses are 7-fold higher following oral
564 administration than those obtained under other conditions.
- 565 **Ergot-Containing Drugs:** Ergot-containing drugs have been reported to cause prolonged
566 vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use
567 of ergotamine-containing or ergot-type medications (e.g., dihydroergotamine, methysergide) and
568 TREXIMET within 24 hours of each other should be avoided (see CONTRAINDICATIONS).
- 569 **Methotrexate:** Caution should be used if TREXIMET is administered concomitantly with
570 methotrexate. Naproxen sodium and other NSAIDs have been reported to reduce the tubular
571 secretion of methotrexate in an animal model, possibly increasing the toxicity of methotrexate.

572 Concomitant administration of some NSAIDs with high-dose methotrexate therapy has been
573 reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe
574 hematologic and gastrointestinal toxicity.

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

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

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

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

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

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

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

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

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

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

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

617 Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).
618 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** The
619 carcinogenic potential of TREXIMET has not been studied.

620 The carcinogenic potential of sumatriptan was evaluated in oral carcinogenicity studies in
621 mice (78 weeks) and rats (104 weeks). The highest dose administered to mice and rats
622 (160 mg/kg/day) is approximately 9 and 18 times, respectively, the recommended human oral
623 daily dose of 85 mg sumatriptan on a mg/m² basis. There was no evidence of an increase in
624 tumors in either species related to sumatriptan administration.

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

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

633 The combination of sumatriptan and naproxen sodium was negative in an in vitro mouse
634 lymphoma tk assay in the presence and absence of metabolic activation. However, in separate in
635 vitro mouse lymphoma tk assays, naproxen sodium alone was reproducibly positive in the
636 presence of metabolic activation.

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

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

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

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

649 In a study in which male and female rats were dosed daily with oral sumatriptan prior to and
650 throughout the mating period, there was a treatment-related decrease in fertility secondary to a

651 decrease in mating in animals treated with 50 and 500 mg/kg/day. The highest no-effect dose for
652 this finding was 5 mg/kg/day, or approximately 0.5 times the recommended human oral daily
653 dose of 85 mg sumatriptan on a mg/m² basis. It is not clear whether the problem is associated
654 with treatment of the males or females or both combined. In a similar study of sumatriptan by the
655 subcutaneous route there was no evidence of impaired fertility at doses up to 60 mg/kg/day.

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

671 In previous developmental toxicity studies in rats and rabbits, oral treatment with sumatriptan
672 was associated with embryoletality, fetal abnormalities, and pup mortality. Oral treatment of
673 pregnant rats with sumatriptan during the period of organogenesis resulted in an increased
674 incidence of fetal blood vessel (cervicothoracic and umbilical) abnormalities and decreased pup
675 survival at doses of 250 mg/kg/day or higher. The highest no-effect dose was approximately
676 60 mg/kg/day, which is approximately 7 times the recommended human oral daily dose of 85 mg
677 sumatriptan on a mg/m² basis. Oral treatment of pregnant rabbits with sumatriptan during the
678 period of organogenesis resulted in an increased incidence of cervicothoracic vascular and
679 skeletal abnormalities at a dose of 50 mg/kg/day and embryoletality at 100 mg/kg/day. The
680 highest no-effect dose for embryotoxicity in rabbits was 15 mg/kg/day, or approximately 3 times
681 the recommended human oral daily dose of 85 mg sumatriptan on a mg/m² basis.

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

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

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

688 **Pregnancy Registry:** To monitor fetal outcomes of pregnant women exposed to
689 TREXIMET, GlaxoSmithKline maintains a TREXIMET Pregnancy Registry. Physicians are

690 encouraged to register patients as soon as possible after they become pregnant and (if possible)
691 before the outcome of the pregnancy is known by calling (800) 336-2176.

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

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

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

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

707 **ADVERSE REACTIONS**

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

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

717

718 **Table 2. Treatment-Emergent Adverse Events Reported by at Least 2% of Patients in 2**
 719 **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

720 * Events that occurred at a frequency of 2% or more in the group treated with TREXIMET
 721 and that occurred more frequently in the group treated with TREXIMET than in the
 722 placebo group.

723

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

772 **Renal and Urinary Disorders:** Infrequent was nephrolithiasis. Rare was renal
773 insufficiency.

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

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

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

780 **DRUG ABUSE AND DEPENDENCE**

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

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

785 **OVERDOSAGE**

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

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

792 Patients (N = 670) have received single oral doses of 140 to 300 mg of sumatriptan without
793 significant adverse effects. Volunteers (N = 174) have received single oral doses of 140 to
794 400 mg without serious adverse events. Overdose of sumatriptan in animals has been fatal and
795 has been heralded by convulsions, tremor, paralysis, inactivity, ptosis, erythema of the
796 extremities, abnormal respiration, cyanosis, ataxia, mydriasis, salivation, and lacrimation.

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

806 In animals 0.5 g/kg of activated charcoal was effective in reducing plasma levels of naproxen.
807 Patients should be managed by symptomatic and supportive care. There are no specific antidotes.
808 Hemodialysis does not decrease the plasma concentration of naproxen because of the high
809 degree of its protein binding. It is unknown what effect hemodialysis or peritoneal dialysis has
810 on the serum concentrations of sumatriptan. Emesis and/or activated charcoal (60 to 100 g in
811 adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within
812 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalization
813 of urine, or hemoperfusion may not be useful due to high protein binding.

814 **DOSAGE AND ADMINISTRATION**

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

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

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

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

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

832 The combined use of TREXIMET with MAO-A inhibitors or use of TREXIMET within
833 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated (see
834 CONTRAINDICATIONS, CLINICAL PHARMACOLOGY: Drug Interactions,
835 PRECAUTIONS: Drug Interactions).

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

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

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

845 **HOW SUPPLIED**

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

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

852 **ANIMAL TOXICOLOGY**

853 **Corneal Opacities:** Dogs receiving oral sumatriptan developed corneal opacities and defects
854 in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day,
855 and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a
856 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses
857 were not established; the lowest dose tested is approximately 0.8 times the recommended human

858 oral daily dose of 85 mg sumatriptan on a mg/m² basis. There was evidence of alterations in
859 corneal appearance on the first day of intranasal dosing to dogs at all doses tested.

860 **PATIENT INFORMATION**

861

862

MEDICATION GUIDE

863

TREXIMET™ [trex' i-met] Tablets

864

(sumatriptan and naproxen sodium)

865

866

What is the most important information I should know about TREXIMET?

867

868

TREXIMET, which contains sumatriptan and naproxen sodium [a nonsteroidal anti-inflammatory drug (NSAID)], may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

869

870

871

- with longer use of NSAID medicines

872

- in people who have heart disease.

873

874

NSAID-containing medicines, such as TREXIMET, should never be used right before or after a heart surgery called a coronary artery bypass graft (CABG).

875

876

877

NSAID-containing medicines, such as TREXIMET, can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

878

879

- can happen without warning symptoms

880

- may cause death.

881

882

The chance of a person getting an ulcer or bleeding increases with:

883

- the use of medicines called steroid hormones (corticosteroids) and blood thinners (anticoagulants)

884

885

- longer use

886

- more frequent use

887

- smoking

888

- drinking alcohol

889

- older age

890

- having poor health.

891

892

TREXIMET is not recommended for people with risk factors for heart disease unless a heart exam is done and shows no problems.

893

894

895

The risk factors for heart disease include:

896

- high blood pressure

- 897 • high cholesterol levels
- 898 • smoking
- 899 • obesity
- 900 • diabetes
- 901 • family history of heart disease
- 902 • female who has gone through menopause
- 903 • male over age 40.

904

905 **“Serotonin syndrome” is a serious and life-threatening problem that may occur with**
906 **TREXIMET, especially if used with antidepressant medicines** called selective serotonin
907 reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs).

908

909 **Commonly used SSRIs are:**

- 910 • CELEXA[®] (citalopram HBr)
- 911 • LEXAPRO[®] (escitalopram oxalate)
- 912 • PAXIL[®] (paroxetine)
- 913 • PROZAC[®]/SARAFEM[®] (fluoxetine)
- 914 • SYMBYAX[®] (olanzapine/fluoxetine)
- 915 • ZOLOFT[®] (sertraline)
- 916 • LUVOX[®] (fluvoxamine).

917

918 **Commonly used SNRIs are:**

- 919 • CYMBALTA[®] (duloxetine)
- 920 • EFFEXOR[®] (venlafaxine).

921

922 **Call your healthcare provider if you have symptoms of serotonin syndrome, which**
923 **include:**

- 924 • mental changes (hallucinations, agitation, coma)
- 925 • fast heartbeat
- 926 • changes in blood pressure
- 927 • high body temperature or sweating
- 928 • tight muscles
- 929 • trouble walking
- 930 • nausea, vomiting, diarrhea.

931

932 **TREXIMET should only be used:**

- 933 • exactly as prescribed
- 934 • at the lowest dose possible for your treatment
- 935 • for the shortest time needed.

936

937 **TREXIMET already contains an NSAID (naproxen). Do not use TREXIMET with other**
938 **medicines to lessen pain or fever without talking to your healthcare provider first,**
939 **because they may contain an NSAID also.**

940

941 **What is TREXIMET?**

942 TREXIMET is a prescription medicine used to treat migraine attacks in adults. It does not
943 prevent or lessen the number of migraines you have, and it is not for other types of headaches.
944 TREXIMET contains 2 medicines: sumatriptan and naproxen sodium (an NSAID). This
945 Medication Guide provides important information you need to know before taking
946 TREXIMET. It does not take the place of talking with your healthcare provider about your
947 medical condition or your treatment.

948

949 **How should I take TREXIMET?**

- 950 • Take 1 TREXIMET tablet to treat your migraine headache. Do not take more than 2
951 TREXIMET tablets in 24 hours. Doses should be separated by at least 2 hours.
952 • TREXIMET can be taken with or without food.
953 • Do not split, crush, or chew TREXIMET tablets.
954 • If you take too much TREXIMET, call the Poison Control Center at 1-800-222-1222.

955

956 **Who should not take TREXIMET?**

957

958 **Do not take TREXIMET right before or after heart bypass surgery.**

959

960 **Do not take TREXIMET if you have or have had:**

- 961 • uncontrolled high blood pressure
962 • hemiplegic or basilar migraine. (Ask your doctor if you are not sure what type of
963 migraine you have.)
964 • liver problems
965 • an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID
966 medicine
967 • a heart attack or a history or symptoms of heart disease (such as chest pain or angina)
968 • a stroke, mini-stroke (transient ischemic attack or TIA), or other stroke-like syndrome
969 • problems with blood circulation to parts of your body, such as less blood flow to your
970 intestines (ischemic bowel disease)
971 • allergic reactions to sumatriptan, naproxen, or other ingredients in TREXIMET.

972

973 **Do not take TREXIMET if you take or have taken an antidepressant medicine called a**
974 **monoamine oxidase (MAO) inhibitor within the last 2 weeks.** Common MAO inhibitors
975 are isocarboxazid (MARPLAN[®]), phenelzine (NARDIL[®]), tranylcypromine (PARNATE[®]),

976 and selegiline (ELDEPRYL[®], EMSAM[®]). Ask your healthcare provider if you are not sure if
977 your medicine is an MAO inhibitor.

978

979 **Do not take TREXIMET if you have taken other migraine medicines in the last 24 hours**
980 **such as:**

- 981 • ergotamine-containing medicine or
- 982 • another triptan medicine.

983

984 **Before starting TREXIMET, tell your healthcare provider about:**

- 985 • all of your medical conditions including kidney or liver problems
- 986 • all allergies to any medicines
- 987 • chest pain, shortness of breath, irregular heartbeats
- 988 • medicines you may take for migraines, depression, or other health problems such as
- 989 MAO inhibitors, SSRIs, or SNRIs
- 990 • all the prescription and non-prescription medicines you take, including vitamins and
- 991 herbal supplements. Some medicines can interact with TREXIMET and cause serious
- 992 side effects.

993

994 **Keep a list of your medicines to show to your healthcare provider.**

995

996 **Before starting TREXIMET, tell your healthcare provider if you:**

- 997 • are pregnant, think you might be pregnant, or are trying to become pregnant.
- 998 **TREXIMET should not be used by pregnant women late in their pregnancy.**
- 999 • are breastfeeding
- 1000 • have a headache that is different from your usual migraine
- 1001 • have or have had epilepsy or seizures.

1002

1003 **What are the possible side effects of TREXIMET?**

1004

<p>Serious side effects include:</p> <ul style="list-style-type: none">• heart attack• heart beat problems• stroke• high blood pressure• heart failure from body swelling (fluid retention)• kidney problems including kidney failure• bleeding and ulcers in the stomach and intestine• low red blood cells (anemia)• life-threatening skin reactions• life-threatening allergic reactions• liver problems including liver failure• asthma attacks in people who have asthma• loss of blood circulation to areas of your body• serotonin syndrome (See list of symptoms in “What is the most important information I should know about TREXIMET?”)	<p>Other side effects include:</p> <ul style="list-style-type: none">• pain, tightness, or pressure in the chest, neck, and throat• stomach pain• constipation• diarrhea• gas• heartburn• nausea• vomiting• dizziness• drowsiness• tiredness• weakness• tingling and numbness• unusual body sensations• redness of face (flushed)
---	--

1005

1006

Get emergency help right away if you have any of the following symptoms:

1007

- shortness of breath or trouble breathing

1008

- chest pain

1009

- swelling of the face or throat

1010

- weakness in one part or on one side of your body

1011

- slurred speech.

1012

1013

Stop TREXIMET and call your healthcare provider right away if you have any of the following symptoms:

1014

1015

- nausea that seems out of proportion to your migraine

1016

- stomach pain

1017

- sudden/severe pain in your belly

1018

- vomit blood

1019

- blood in your bowel movement or it is black and sticky like tar

1020

- itching

1021

- skin rash or blisters with fever

1022

- yellow skin or eyes

1023

- swelling of the arms and legs, hands, feet, face, lips, or tongue

1024

- unusual weight gain

1025

- more tired or weaker than usual

1026

- flu-like symptoms

- 1027 • serotonin syndrome. See list of symptoms in “What is the most important information I
1028 should know about TREXIMET?”

1029

1030 Tell you healthcare provider if you have any side effects that bother you or do not go away.
1031 These are not all of the side effects of TREXIMET. For more information ask your healthcare
1032 provider.

1033

1034 Call your healthcare provider for medical advice about side effects. You may report side
1035 effects at FDA at 1-800-FDA-1088.

1036

1037 **How should I store TREXIMET?**

- 1038 • Store TREXIMET at room temperature, 59° to 86°F (15° to 30°C).
1039 • Keep TREXIMET and all medicines out of the reach of children.

1040

1041 **General information about TREXIMET**

- 1042 • Medicines are sometimes prescribed for purposes other than those listed in a Medication
1043 Guide. Do not use TREXIMET for a condition for which it was not prescribed.
1044 • Do not give TREXIMET to other people, even if they have the same problem you have. It
1045 may harm them.
1046 • This Medication Guide contains the most important information about TREXIMET. If you
1047 would like more information, talk with your healthcare provider.
1048 • You can ask your healthcare provider for information written for healthcare professionals.
1049 • For more information call 1-888-825-5249 (toll-free), or visit www.TREXIMET.com.

1050

1051 **What are the ingredients in TREXIMET?**

1052 **Active ingredients:** sumatriptan succinate and naproxen sodium

1053 **Inactive ingredients:** croscarmellose sodium, dextrose monohydrate, dibasic calcium
1054 phosphate, FD&C Blue No. 2, lecithin, magnesium stearate, maltodextrin, microcrystalline
1055 cellulose, povidone, sodium bicarbonate, sodium carboxymethylcellulose, talc, and titanium
1056 dioxide.

1057

1058 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

1059

1060 April 2008

TRX:1MG

1061

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1063 trademarks of GlaxoSmithKline.

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1065 GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse
1066 GlaxoSmithKline or its products.

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1069

1070 GlaxoSmithKline

1071 Research Triangle Park, NC 27709

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1075 April 2008

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/s/

Russell Katz
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