

PRESCRIBING INFORMATION

TREXIMET[®]
(sumatriptan and naproxen sodium)
Tablets

WARNINGS

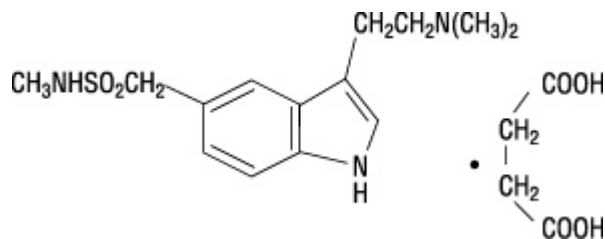
Cardiovascular Risk: TREXIMET may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater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

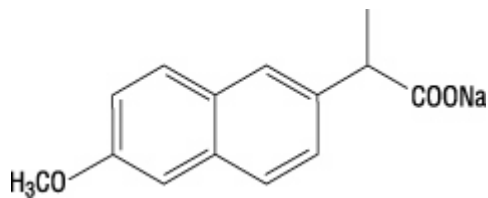
TREXIMET contains sumatriptan (as the succinate), a selective 5-hydroxytryptamine₁ (5-HT₁) receptor subtype agonist, and naproxen sodium, a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs).

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:



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 5-
54 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}
64 (median, range) for sumatriptan following administration of TRIXIMET occurs at
65 approximately 1 hour (0.3 to 4.0 hours). C_{max} (median, range) for naproxen following
66 administration of TRIXIMET occurs at approximately 5 hours (0.3 to 12 hours). The
67 sumatriptan half-life is approximately 2 hours (15% to 43% CV) and the naproxen half-life is

68 approximately 19 hours (13% to 15% CV). The mean C_{max} for sumatriptan when given as
69 TREXIMET is similar to that of sumatriptan when given as IMITREX[®] (sumatriptan succinate)
70 Tablets 100 mg alone. The median sumatriptan T_{max} is only slightly different (1 hour for
71 TREXIMET and 1.5 hours for IMITREX). The C_{max} for naproxen is approximately 36% lower,
72 and the T_{max} occurs approximately 4 hours later from TREXIMET than from ANAPROX[®] DS
73 (naproxen sodium tablets) 550 mg. AUC values for sumatriptan and for naproxen are similar for
74 TREXIMET compared to IMITREX or ANAPROX DS, respectively. In a crossover study in 16
75 patients, the pharmacokinetics of both components administered as TREXIMET were similar
76 during a migraine attack and during a migraine-free 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. No rescue medication was allowed within 2 hours
155 postdose. Patients evaluated their headache pain 2 hours after taking 1 dose of study medication;
156 headache relief was defined as a reduction in headache severity from moderate or severe pain to
157 mild or no pain. Associated symptoms of nausea, photophobia, and phonophobia were also
158 evaluated. Sustained pain free was defined as a reduction in headache severity from moderate or
159 severe pain to no pain at 2 hours postdose without a return of mild, moderate, or severe pain and
160 no use of rescue medication for 24 hours postdose. The results from the 2 controlled clinical
161 trials are summarized in Table 1. In both trials, the percentage of patients achieving headache
162 pain relief 2 hours after treatment was significantly greater among patients receiving
163 TREXIMET (65% and 57%) compared with those who received placebo (28% and 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^a**

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

171 ^aP values provided only for prespecified comparisons.

172 ^bP<0.05 versus placebo and sumatriptan.

173 ^cP<0.01 versus placebo, sumatriptan, and naproxen sodium.

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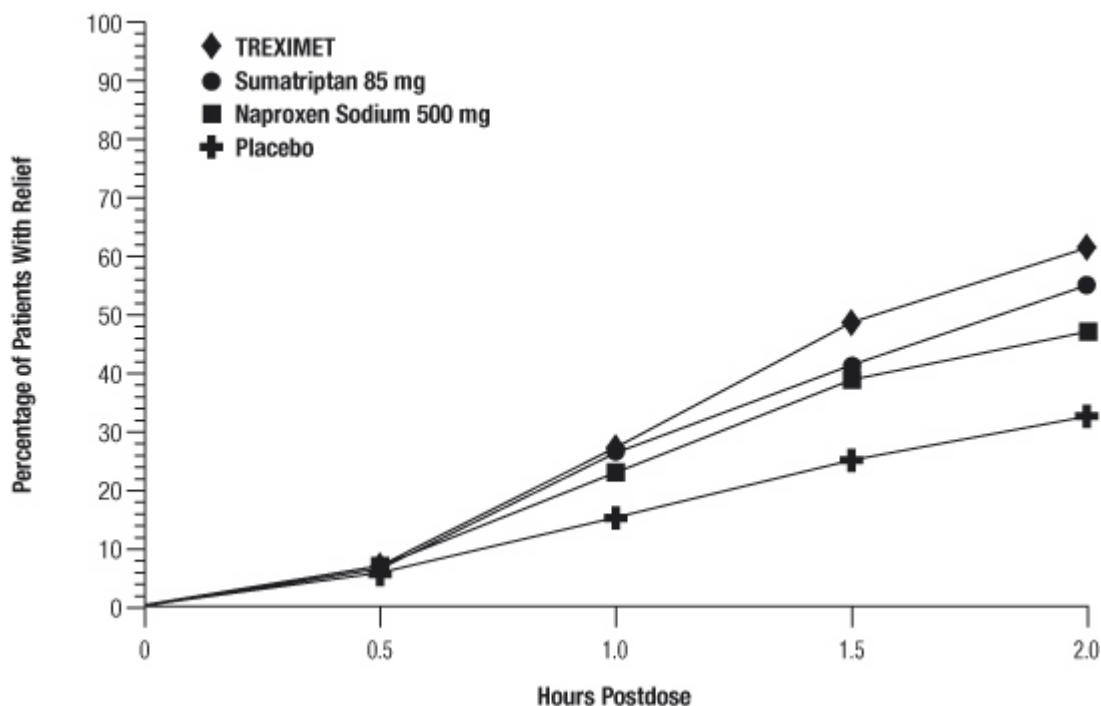
175 Note that comparisons of the performance of different drugs based upon results
176 obtained in different clinical trials are never reliable. Because studies are generally
177 conducted at different times, with different samples of patients, by different investigators,
178 employing different criteria 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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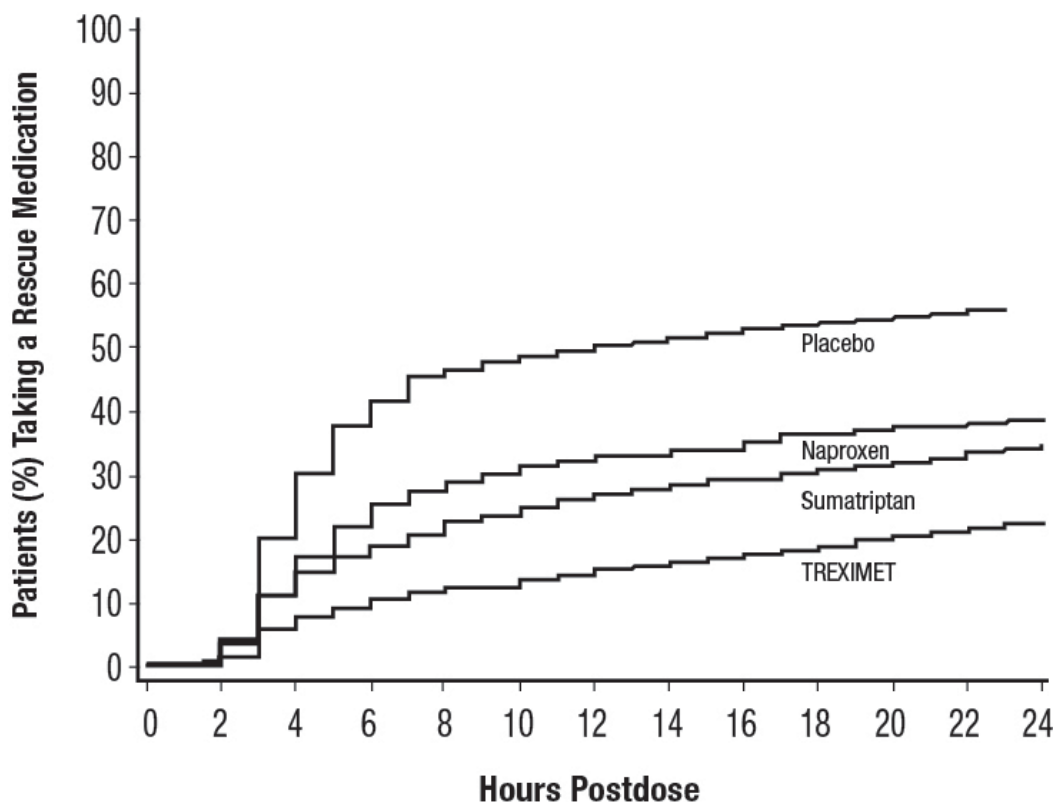
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189 Compared with placebo, there was a decreased incidence of photophobia, phonophobia, and
190 nausea 2 hours after the administration of TREXIMET. The estimated probability of taking a
191 rescue medication over the first 24 hours is shown in Figure 2.

192

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



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

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 NSAIDs should be given with care to patients with a history of inflammatory bowel disease
397 (ulcerative colitis, Crohn's disease) as their condition may be exacerbated.

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

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

411 **Anaphylactic/Anaphylactoid Reactions:** As with other NSAID-containing products,
412 anaphylactic/anaphylactoid reactions may occur in patients without known prior exposure to
413 naproxen. TREXIMET should not be given to patients with the aspirin triad. This symptom
414 complex typically occurs in patients with asthma who experience rhinitis with or without nasal
415 polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other
416 NSAIDs (see CONTRAINDICATIONS, PRECAUTIONS: Preexisting Asthma, and
417 PRECAUTIONS: Drug Interactions).

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

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

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

432 **PRECAUTIONS**

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

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

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

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

452 **Other Potentially Serious Neurologic Conditions:** Care should be taken to exclude other
453 potentially serious neurologic conditions before treating headache in patients not previously
454 diagnosed with migraine headache or who experience a headache that is atypical for them. There
455 have been reports where patients received sumatriptan for severe headaches that were
456 subsequently shown to have been secondary to an evolving neurologic lesion (see WARNINGS:
457 Drug-Associated Cerebrovascular Events and Fatalities). For a given attack, if a patient does not
458 respond to the first dose of TREXIMET, the diagnosis of migraine should be reconsidered before
459 administration of a second dose.

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

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

483 **Binding to Melanin-Containing Tissues:** In rats treated with a single subcutaneous dose
484 (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half-life of
485 radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or
486 its metabolites bind to the melanin of the eye. Because there could be an accumulation in
487 melanin-rich tissues over time, sumatriptan could possibly cause toxicity in these tissues after
488 extended use. However, no effects on the retina related to treatment with sumatriptan were noted

489 in any of the oral or subcutaneous toxicity studies. Although no systematic monitoring of
490 ophthalmologic function was undertaken in clinical trials and no specific recommendations for
491 ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-
492 term ophthalmologic effects.

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

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

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

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

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

525 1. TREXIMET may cause serious cardiovascular side effects such as myocardial infarction or
526 stroke, which may result in hospitalization and even death. Although serious cardiovascular
527 events can occur without warning symptoms, patients should be alert for the signs and
528 symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for

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

568 manifestations occur (e.g., eosinophilia, rash), or abnormal liver tests persist or worsen,
569 TREXIMET should be discontinued.

570 **Drug Interactions: Monoamine Oxidase-A Inhibitors:** The use of TREXIMET in patients
571 receiving MAO-A inhibitors is contraindicated (see CLINICAL PHARMACOLOGY: Drug
572 Interactions and CONTRAINDICATIONS). MAO-A inhibitors reduce sumatriptan clearance,
573 significantly increasing systemic exposure. In patients taking MAO-A inhibitors, sumatriptan
574 plasma levels attained after treatment with recommended doses are 7-fold higher following oral
575 administration than those obtained under other conditions.

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

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

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

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

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

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

604 **Lithium:** NSAIDs have produced an elevation of plasma lithium levels and a reduction in
605 renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal
606 clearance was decreased by approximately 20%. These effects have been attributed to inhibition

607 of renal prostaglandin synthesis by the NSAID. Thus, when TREXIMET and lithium are
608 administered concurrently, patients should be observed carefully for signs of lithium toxicity.

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

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

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

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

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

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

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

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

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

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

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

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

646 vitro mouse lymphoma tk assays, naproxen sodium alone was reproducibly positive in the
647 presence of metabolic activation.

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

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

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

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

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

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

682 In previous developmental toxicity studies in rats and rabbits, oral treatment with sumatriptan
683 was associated with embryoletality, fetal abnormalities, and pup mortality. Oral treatment of
684 pregnant rats with sumatriptan during the period of organogenesis resulted in an increased
685 incidence of fetal blood vessel (cervicothoracic and umbilical) abnormalities and decreased pup

686 survival at doses of 250 mg/kg/day or higher. The highest no-effect dose was approximately
687 60 mg/kg/day, which is approximately 7 times the recommended human oral daily dose of 85 mg
688 sumatriptan on a mg/m² basis. Oral treatment of pregnant rabbits with sumatriptan during the
689 period of organogenesis resulted in an increased incidence of cervicothoracic vascular and
690 skeletal abnormalities at a dose of 50 mg/kg/day and embryoletality at 100 mg/kg/day. The
691 highest no-effect dose for embryotoxicity in rabbits was 15 mg/kg/day, or approximately 3 times
692 the recommended human oral daily dose of 85 mg sumatriptan on a mg/m² basis.

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

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

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

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

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

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

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

714 **ADVERSE REACTIONS**

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

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

724

725 **Table 2. Treatment-Emergent Adverse Events Reported by at Least 2% of Patients in 2**
726 **Controlled Migraine Trials^a**

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

727 ^a Events that occurred at a frequency of 2% or more in the group treated with TREXIMET
728 and that occurred more frequently in the group treated with TREXIMET than in the
729 placebo group.

730

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

779 **Renal and Urinary Disorders:** Infrequent was nephrolithiasis. Rare was renal
780 insufficiency.

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

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

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

787 **DRUG ABUSE AND DEPENDENCE**

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

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

792 **OVERDOSAGE**

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

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

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

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

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

821 **DOSAGE AND ADMINISTRATION**

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

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

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

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

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

839 The combined use of TREXIMET with MAO-A inhibitors or use of TREXIMET within
840 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated (see
841 CONTRAINDICATIONS, CLINICAL PHARMACOLOGY: Drug Interactions,
842 PRECAUTIONS: Drug Interactions).

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

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

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

852 **HOW SUPPLIED**

853 TREXIMET contains 119 mg of sumatriptan succinate equivalent to 85 mg of sumatriptan
854 and 500 mg of naproxen sodium and is supplied as blue film-coated tablets debossed on one side
855 with *TREXIMET* in bottles of 9 tablets with desiccant (NDC 0173-0750-49).

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

859 **ANIMAL TOXICOLOGY**

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

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

867

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869 ANAPROX is a registered trademark of F. Hoffmann-La Roche Ltd.

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874 Research Triangle Park, NC 27709

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878 October 2012

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MEDICATION GUIDE

882

TREXIMET[®] [*trex' i-met*] Tablets

883

(sumatriptan and naproxen sodium)

884

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

886 **1. TREXIMET may increase your chance of a heart attack or stroke that can lead to**
887 **death. TREXIMET contains 2 medicines: sumatriptan and naproxen sodium (a**
888 **nonsteroidal anti-inflammatory drug [NSAID]).**

889 **Your chance of a heart attack or stroke increases:**

- 890 • with longer use of NSAID medicines
- 891 • if you have heart disease.

892 **2. TREXIMET should never be used right before or after a heart surgery called a**
893 **coronary artery bypass graft (CABG).**

894 **3. TREXIMET can cause ulcers and bleeding in the stomach and intestines at any time**
895 **during your treatment.**

896 **Ulcers and bleeding:**

- 897 • can happen without warning symptoms
- 898 • may cause death.

899 **Your chance of getting an ulcer or bleeding increases with:**

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

- 902 • longer use
- 903 • more frequent use
- 904 • smoking
- 905 • drinking alcohol
- 906 • older age
- 907 • having poor health.

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

910 **Risk factors for heart disease include:**

- 911 • high blood pressure
- 912 • high cholesterol levels
- 913 • smoking
- 914 • obesity
- 915 • diabetes
- 916 • family history of heart disease
- 917 • female who has gone through menopause
- 918 • male over age 40.

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

922 **Commonly used SSRIs are:**

- 923 • CELEXA[®] (citalopram HBr)
- 924 • LEXAPRO[®] (escitalopram oxalate)
- 925 • PAXIL[®] (paroxetine)
- 926 • PROZAC[®]/SARAFEM[®] (fluoxetine)
- 927 • SYMBYAX[®] (olanzapine/fluoxetine)
- 928 • ZOLOFT[®] (sertraline)
- 929 • LUVOX[®] (fluvoxamine).

930 **Commonly used SNRIs are:**

- 931 • CYMBALTA[®] (duloxetine)
- 932 • EFFEXOR[®] (venlafaxine).

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

- 935 • mental changes (hallucinations, agitation, coma)
- 936 • fast heartbeat
- 937 • changes in blood pressure
- 938 • high body temperature or sweating
- 939 • tight muscles

- 940 • trouble walking
941 • nausea, vomiting, diarrhea.

942 **6. TREXIMET should only be used:**

- 943 • exactly as prescribed
944 • at the lowest dose possible for your treatment
945 • for the shortest time needed.

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

949

950 **What is TREXIMET?**

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

957

958 **How should I take TREXIMET?**

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

964

965 **Who should not take TREXIMET?**

966 Do not take TREXIMET right before or after heart bypass surgery. Do not take TREXIMET if
967 you have or have had:

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

978 **Do not take TREXIMET if you take or have taken an antidepressant medicine called a**
979 **monoamine oxidase (MAO) inhibitor within the last 2 weeks.** Common MAO inhibitors are
980 isocarboxazid (MARPLAN[®]), phenelzine (NARDIL[®]), tranylcypromine (PARNATE[®]), and
981 selegiline (ELDEPRYL[®], EMSAM[®]). Ask your healthcare provider if you are not sure if your
982 medicine is an MAO inhibitor.

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

- 985 • ergotamine-containing medicine or
- 986 • another triptan medicine.

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

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

995 **Keep a list of your medicines to show to your healthcare provider. Before starting**
996 **TREXIMET, tell your healthcare provider if you:**

- 997 • are pregnant, think you might be pregnant, or are trying to become pregnant. **TREXIMET**
998 **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?**

Serious side effects include:

- heart attack
- heartbeat 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?”)

Other side effects include:

- 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)

1004 **Get emergency help right away if you have any of the following symptoms:**

- 1005 • shortness of breath or trouble breathing
- 1006 • chest pain
- 1007 • swelling of the face or throat
- 1008 • weakness in one part or on one side of your body
- 1009 • slurred speech.

1010 **Stop TREXIMET and call your healthcare provider right away if you have any of the following symptoms:**

- 1012 • nausea that seems out of proportion to your migraine
- 1013 • stomach pain
- 1014 • sudden/severe pain in your belly
- 1015 • vomit blood
- 1016 • blood in your bowel movement or it is black and sticky like tar
- 1017 • itching
- 1018 • skin rash or blisters with fever
- 1019 • yellow skin or eyes
- 1020 • swelling of the arms and legs, hands, feet, face, lips, or tongue
- 1021 • unusual weight gain
- 1022 • more tired or weaker than usual
- 1023 • flu-like symptoms
- 1024 • serotonin syndrome. See list of symptoms in “What is the most important information I should know about TREXIMET?”
- 1025

1026 Tell your healthcare provider if you have any side effects that bother you or do not go away.
1027 These are not all of the side effects of TREXIMET. For more information ask your healthcare
1028 provider.

1029 Call your healthcare provider for medical advice about side effects. You may report side effects
1030 to FDA at 1-800-FDA-1088.

1031

1032 **How should I store TREXIMET?**

- 1033 • Store TREXIMET at room temperature, 59° to 86°F (15° to 30°C).
1034 • Keep TREXIMET and all medicines out of the reach of children.

1035

1036 **General information about TREXIMET**

- 1037 • Medicines are sometimes prescribed for purposes other than those listed in a Medication
1038 Guide. Do not use TREXIMET for a condition for which it was not prescribed.
1039 • Do not give TREXIMET to other people, even if they have the same problem you have. It
1040 may harm them.
1041 • This Medication Guide contains the most important information about TREXIMET. If you
1042 would like more information, talk with your healthcare provider.
1043 • You can ask your healthcare provider for information written for healthcare professionals.
1044 • For more information call 1-888-825-5249 (toll-free), or visit www.TREXIMET.com.

1045

1046 **What are the ingredients in TREXIMET?**

1047 **Active ingredients:** sumatriptan succinate and naproxen sodium

1048 **Inactive ingredients:** croscarmellose sodium, dextrose monohydrate, dibasic calcium
1049 phosphate, FD&C Blue No. 2, lecithin, magnesium stearate, maltodextrin, microcrystalline
1050 cellulose, povidone, sodium bicarbonate, sodium carboxymethylcellulose, talc, and titanium
1051 dioxide.

1052

1053 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

1054

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