

1 PRESCRIBING INFORMATION

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

5 **WARNINGS**

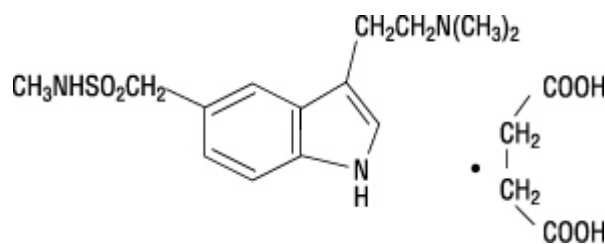
6 **Cardiovascular Risk:** TREXIMET may cause an increased risk of serious cardiovascular
7 thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may
8 increase with duration of use. Patients with cardiovascular disease or risk factors for
9 cardiovascular disease may be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

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

18 **DESCRIPTION**

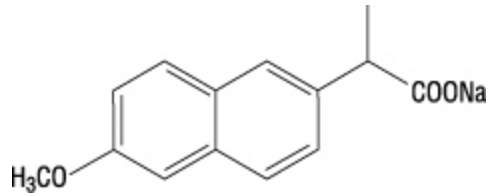
19 TREXIMET contains sumatriptan (as the succinate), a selective 5-hydroxytryptamine₁
20 (5-HT₁) receptor subtype agonist, and naproxen sodium, a member of the arylacetic acid group
21 of nonsteroidal anti-inflammatory drugs (NSAIDs).

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



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

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



32
33

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

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

42 CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

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

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

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

101 Naproxen is extensively metabolized to 6-O-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-O-desmethyl naproxen (less

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

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

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

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

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

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

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

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

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

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

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

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

148 **CLINICAL TRIALS**

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

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

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

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

171 * p values provided only for prespecified comparisons.
 172 † p<0.05 versus placebo and sumatriptan.
 173 ‡ p<0.01 versus placebo, sumatriptan, and naproxen sodium.

174

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