PRESCRIBING INFORMATION

TREXIMET®

(sumatriptan and naproxen sodium)
Tablets

WARNINGS

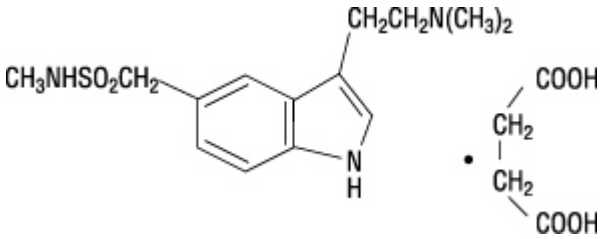
Cardiovascular Risk: TREXIMET may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater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

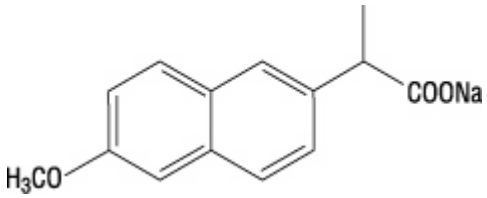
TREXIMET contains sumatriptan (as the succinate), a selective 5-hydroxytryptamine$_1$ (5-HT$_1$) receptor subtype agonist, and naproxen sodium, a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs).

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 $C_{14}H_{21}N_3O_2S \bullet C_4H_6O_4$, 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:



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

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

CLINICAL PHARMACOLOGY

Mechanism of Action: TREXIMET contains sumatriptan, a 5-HT_1 receptor agonist that mediates vasoconstriction of the human basilar artery and vasculature of human dura mater, which correlates with the relief of migraine headache. It also contains naproxen, an NSAID that inhibits the synthesis of inflammatory mediators. Therefore, sumatriptan and naproxen contribute to the relief of migraine through pharmacologically different mechanisms of action.

Sumatriptan is a 5-HT_1 receptor agonist that binds with high affinity to 5-HT_{1B} and 5-HT_{1D} receptors. Sumatriptan has only a weak affinity for 5-HT_{1A}, 5-HT_{5A}, and 5-HT_7 receptors and no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT_2, 5-HT_3, or 5-HT_4 receptor subtypes or at $alpha_1$-, $alpha_2$-, or beta-adrenergic; $dopamine_1$; $dopamine_2$; muscarinic; or benzodiazepine receptors. In addition to causing vasoconstriction, experimental data from animal studies show that sumatriptan also activates 5-HT_1 receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels. Such an action may contribute to the antimigrainous effect of sumatriptan in humans. In the anesthetized dog, sumatriptan selectively reduces carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance.

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

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

approximately 19 hours (13% to 15% CV). The mean C_{max} for sumatriptan when given as TREXIMET is similar to that of sumatriptan when given as IMITREX® (sumatriptan succinate) Tablets 100 mg alone. The median sumatriptan T_{max} is only slightly different (1 hour for TREXIMET and 1.5 hours for IMITREX). The C_{max} for naproxen is approximately 36% lower, and the T_{max} occurs approximately 4 hours later from TREXIMET than from ANAPROX® DS (naproxen sodium tablets) 550 mg. AUC values for sumatriptan and for naproxen are similar for TREXIMET compared to IMITREX or ANAPROX DS, respectively. In a crossover study in 16 patients, the pharmacokinetics of both components administered as TREXIMET were similar during a migraine attack and during a migraine-free period.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gender: In a pooled analysis of 5 pharmacokinetic studies, there was no effect of gender on the systemic exposure of TREXIMET. In a study comparing the pharmacokinetics of sumatriptan in females and males, no differences were observed between genders for AUC, C_{max}, T_{max}, and $T_{½}$.

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

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

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

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

CLINICAL TRIALS

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

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

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

[a] *P* values provided only for prespecified comparisons.

[b] $P<0.05$ versus placebo and sumatriptan.

[c] $P<0.01$ versus placebo, sumatriptan, and naproxen sodium.

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