HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TREXIMET safely and effectively. See full prescribing information for TREXIMET.

TREXIMET (sumatriptan and naproxen sodium) tablets, for oral use
Initial U.S. Approval: 2008

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. (5.1)**
- **TREXIMET is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) 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 and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5.2)**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.14) 11/2024

---------- INDICATIONS AND USAGE----------

TREXIMET is a combination of sumatriptan, a serotonin (5-HT) 1b/1d receptor agonist (triptan), and naproxen sodium, a non-steroidal anti-inflammatory drug, indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older. (1)

Limitations of Use:

- Use only if a clear diagnosis of migraine headache has been established. (1)
- Not indicated for the prophylactic therapy of migraine attacks. (1)
- Not indicated for the treatment of cluster headache. (1)

----------DOSAGE AND ADMINISTRATION----------

Adults

- Recommended dosage: 1 tablet of 85/500 mg. (2.1)
- Maximum dosage in a 24-hour period: 2 tablets of 85/500 mg; separate doses by at least 2 hours. (2.1)

Pediatric Patients 12 to 17 years of Age

- Recommended dosage: 1 tablet of 10/60 mg. (2.2)
- Maximum dosage in a 24-hour period: 1 tablet of 85/500 mg.

Mild to Moderate Hepatic Impairment

- Recommended dosage: 1 tablet of 10/60 mg. (2.3, 8.7)

---------- DOSAGE FORMS AND STRENGTHS----------

Tablets: 85 mg sumatriptan / 500 mg naproxen sodium (3)
10 mg sumatriptan / 60 mg naproxen sodium (3)

---------- CONTRAINDICATIONS ----------

- History of coronary artery disease or coronary vasospasm. (4)
- In the setting of CABG surgery. (4)
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders. (4)
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine. (4)
- Peripheral vascular disease. (4)
- Ischemic bowel disease. (4)
- Uncontrolled hypertension. (4)
- Recent (within 24 hours) use of another 5-HT_1 agonist (e.g., another triptan) or of ergotamine-containing medication. (4)
- Concurrent or recent (past 2 weeks) use of monoamine oxidase-A inhibitor. (4)
- History of asthma, urticaria, other allergic type reactions, rhinitis, or nasal polyps syndrome after taking aspirin or other NSAID/analgesic drugs. (4)
- Known hypersensitivity to sumatriptan, naproxen, or any components of TREXIMET (angioedema and anaphylaxis seen). (4)
- Severe hepatic impairment. (4)

---------- WARNINGS and PRECAUTIONS ----------

- Cardiovascular Thrombotic Events: Perform cardiac evaluation in patients with cardiovascular risk factors. (5.1)
- Arrhythmias: Discontinue TREXIMET if occurs. (5.3)
- Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure: Generally not associated with myocardial ischemia; evaluate for coronary artery disease in patients at high risk. (5.4)
- Cerebrovascular Events: Discontinue TREXIMET if occurs. (5.5)
- Other Vasospasm Reactions: Discontinue TREXIMET if non-coronary vasospastic reaction occurs. (5.6)
- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop. (5.7)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure. (5.8)
- Heart Failure and Edema: Avoid use of TREXIMET in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure. (5.9)
- Medication Overuse Headache: Detoxification may be necessary. (5.10)
- Serotonin Syndrome: Discontinue TREXIMET if occurs. (5.11)
- Renal Toxicity and Hyperkalemia: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of TREXIMET in patients with advanced renal disease. (5.12)
- Anaphylactic Reactions: TREXIMET should not be given to patients with the aspirin triad. Seek emergency help if an anaphylactic reaction occurs. (5.13)
- Serious Skin Reactions: Discontinue TREXIMET at first sign of rash or other signs of hypersensitivity. (5.14)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically. (5.15)
- Fetal Toxicity: Limit use of NSAIDs, including TREXIMET, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus. (5.16, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. (5.17)
- Exacerbation of Asthma Related to Aspirin Sensitivity: TREXIMET is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity). (5.18)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (incidence ≥2%) were:

- Adults: Dizziness, somnolence, nausea, chest discomfort/chest pain, neck/throat/jaw pain/tightness/pressure, paresthesia, dyspepsia, dry mouth. (6.1)
- Pediatrics: Hot flush (i.e., hot flash[es]) and muscle tightness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Currax Pharmaceuticals LLC at 1-800-793-2145 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking TREXIMET with drugs that interfere with hemostasis. Concomitant use of TREXIMET and analgesic doses of aspirin is not generally recommended. (7.1)
- ACE Inhibitors and ARBs: Concomitant use with TREXIMET in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function. (7.1)
- Diuretics: NSAIDs can reduce natriuretic effect of loop and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects. (7.1)
- Digoxin: Concomitant use with TREXIMET can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels. (7.1)
- Lithium: Increases lithium plasma levels. (7.1)
- Methotrexate: Increases methotrexate plasma levels. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of TREXIMET in women who have difficulties conceiving (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 11/2024

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use *[see Warnings and Precautions (5.1)]*.**
- **TREXIMET is contraindicated in the setting of coronary artery bypass graft (CABG) surgery *[see Contraindications (4) Warnings and Precautions (5.1)]*.**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) 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 and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

TREXIMET is indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older.

Limitations of Use:

- Use only if a clear diagnosis of migraine headache has been established. If a patient has no response to the first migraine attack treated with TREXIMET, reconsider the diagnosis of migraine before TREXIMET is administered to treat any subsequent attacks.
- TREXIMET is not indicated for the prevention of migraine attacks.
- Safety and effectiveness of TREXIMET have not been established for cluster headache.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adults

The recommended dosage for adults is 1 tablet of TREXIMET 85/500 mg. TREXIMET 85/500 mg contains a dose of sumatriptan higher than the lowest effective dose. The choice of the dose of sumatriptan, and of the use of a fixed combination such as in TREXIMET 85/500 mg should be made on an individual basis, weighing the possible benefit of a higher dose of sumatriptan with the potential for a greater risk of adverse reactions.

The maximum recommended dosage in a 24-hour period is 2 tablets, taken at least 2 hours apart.

The safety of treating an average of more than 5 migraine headaches in adults in a 30-day period has not been established.

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

2.2 Dosage in Pediatric Patients 12 to 17 Years of Age

The recommended dosage for pediatric patients 12 to 17 years of age is 1 tablet of TREXIMET 10/60 mg.

The maximum recommended dosage in a 24-hour period is 1 tablet of TREXIMET 85/500 mg.

The safety of treating an average of more than 2 migraine headaches in pediatric patients in a 30-day period has not been established.

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

2.3 Dosing in Patients with Hepatic Impairment

TREXIMET is contraindicated in patients with severe hepatic impairment *[see Contraindications (4), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

In patients with mild to moderate hepatic impairment, the recommended dosage in a 24-hour period is 1 tablet of TREXIMET 10/60 mg *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

2.4 Administration Information

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

3 DOSAGE FORMS AND STRENGTHS

10 mg sumatriptan/60 mg naproxen sodium, light-blue film-coated tablets, debossed on one side with “TREXIMET” and the other side with “10-60”.
85 mg sumatriptan/500 mg naproxen sodium, blue film-coated tablets, debossed on one side with “TREXIMET”

4 CONTRAINDICATIONS

TREXIMET is contraindicated in the following patients:

- Ischemic coronary artery disease (CAD) (angina pectoris, history of myocardial infarction, or documented silent ischemia) or coronary artery vasospasm, including Prinzmetal’s angina *[see Warnings and Precautions (5.1)]*.
- In the setting of coronary artery bypass graft (CABG) surgery *[see Warnings and Precautions (5.1)]*.
- Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders *[see Warnings and Precautions (5.3)]*.
- History of stroke or transient ischemic attack (TIA) or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke *[see Warnings and Precautions (5.5)]*.
- Peripheral vascular disease *[see Warnings and Precautions (5.6)]*.
- Ischemic bowel disease *[see Warnings and Precautions (5.6)]*.
- Uncontrolled hypertension *[see Warnings and Precautions (5.8)]*.
- Recent use (i.e., within 24 hours) of ergotamine-containing medication, ergot-type medication (such as dihydroergotamine or methysergide), or another 5-hydroxytryptamine$_1$ (5-HT$_1$) agonist *[see Drug Interactions (7)]*.
- Concurrent administration of a monoamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.
- History of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients *[see Warnings and Precautions (5.13, 5.14, 5.18)]*.
- Known hypersensitivity (e.g., anaphylactic reactions, angioedema, and serious skin reactions) to sumatriptan, naproxen, or any components of TREXIMET *[see Warnings and Precautions (5.14)]*.
- Severe hepatic impairment *[see Warnings and Precautions (5.7), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

The use of TREXIMET is contraindicated in patients with ischemic or vasospastic coronary artery disease (CAD) and in the setting of coronary artery bypass graft (CABG) surgery due to increased risk of serious cardiovascular events with sumatriptan and NSAIDS *[see Contraindications (4)]*.

Cardiovascular Events with Sumatriptan

There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of sumatriptan. Some of these reactions occurred in patients without known CAD. TREXIMET may cause coronary artery vasospasm (Prinzmetal's angina), even in patients without a history of CAD.

Cardiovascular Thrombotic Events with Nonsteroidal Anti-inflammatory Drugs

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as naproxen, increases the risk of serious gastrointestinal (GI) events *[see Warnings and Precautions (5.2)]*.

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG *[see Contraindications (4)]*.

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Perform a cardiovascular evaluation in patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving TREXIMET. If there is evidence of CAD or

coronary artery vasospasm, TREXIMET is contraindicated. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first dose of TREXIMET in a medically supervised setting and performing an electrocardiogram (ECG) immediately following administration of TREXIMET. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of TREXIMET.

Physicians and patients should remain alert for the development of cardiovascular events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular events and the steps to take if they occur.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including naproxen, a component of TREXIMET, cause serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only 1 in 5 patients who develop a serious upper gastrointestinal adverse event on NSAID therapy is symptomatic. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs appear to occur in approximately 1% of patients treated daily for 3 to 6 months and in about 2% to 4% of patients treated for 1 year. However, even short-term therapy is not without risk.

Among 3,302 adult patients with migraine who received TREXIMET in controlled and uncontrolled clinical trials, 1 patient experienced a recurrence of gastric ulcer after taking 8 doses over 3 weeks, and 1 patient developed a gastric ulcer after treating an average of 8 attacks per month over 7 months.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing gastrointestinal bleeding compared with patients with neither of these risk factors. Other factors that increase the risk for gastrointestinal bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal gastrointestinal events occurred in elderly or debilitated patients, and therefore special care should be taken in treating this population. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For high risk patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue TREXIMET until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding *[see Drug Interactions (7)]*.

5.3 Arrhythmias

Life-threatening disturbances of cardiac rhythm, including ventricular tachycardia and ventricular fibrillation leading to death, have been reported within a few hours following the administration of 5-HT_1 agonists. Discontinue TREXIMET if these disturbances occur.

TREXIMET is contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.

5.4 Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure

Sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw commonly occur after treatment with sumatriptan and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. The use of TREXIMET is contraindicated in patients with CAD and those with Prinzmetal's variant angina.

5.5 Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT_1 agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. Also, patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). Discontinue TREXIMET if a cerebrovascular event occurs.

Before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, exclude other potentially serious neurological conditions. TREXIMET is contraindicated in patients with a history of stroke or TIA *[see Contraindications (4)]*.

5.6 Other Vasospasm Reactions

Sumatriptan may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with abdominal pain and bloody diarrhea), splenic infarction, and Raynaud′s syndrome. In patients who experience symptoms or signs suggestive of non-coronary vasospasm reaction following the use of any 5-HT_1 agonist, rule out a vasospastic reaction before receiving additional TREXIMET.

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT_1 agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT_1 agonists have not been clearly established.

5.7 Hepatotoxicity

Borderline elevations of 1 or more liver tests may occur in up to 15% of patients who take NSAIDs including naproxen, a component of TREXIMET. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Notable (3 times the upper limit of normal) elevations of SGPT (ALT) or SGOT (AST) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare, sometimes fatal cases of severe hepatic injury, including jaundice and fatal fulminant hepatitis, liver necrosis, and hepatic failure have been reported with NSAIDs.

TREXIMET is contraindicated in patients with severe hepatic impairment *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with TREXIMET. TREXIMET should be discontinued if clinical signs and symptoms consistent with liver disease develop, if systemic manifestations occur (e.g., eosinophilia, rash), or if abnormal liver tests persist or worsen.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flulike" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if

systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue TREXIMET immediately, and perform a clinical evaluation of the patient.

5.8 Hypertension

Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has been reported on rare occasions in patients treated with 5-HT_1 agonists, including sumatriptan, a component of TREXIMET. This occurrence has included patients without a history of hypertension.

NSAIDs, including naproxen, a component of TREXIMET, can also lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of cardiovascular events. Patients taking angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs *[see Drug Interactions (7)]*.

Monitor blood pressure in patients treated with TREXIMET. TREXIMET is contraindicated in patients with uncontrolled hypertension *[see Contraindications (4)]*.

5.9 Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of naproxen may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) *[see Drug Interactions (7)]*.

Avoid the use of TREXIMET in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If TREXIMET is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Since each TREXIMET 85/500 mg tablet contains approximately 60 mg of sodium and each TREXIMET 10/60 mg tablet contains approximately 20 mg of sodium, this should be considered in patients whose overall intake of sodium must be severely restricted.

5.10 Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or a combination of these drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches, or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

5.11 Serotonin Syndrome

Serotonin syndrome may occur with TREXIMET, particularly during coadministration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors *[see Contraindications (4) and Drug Interactions (7.1)]*. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually

occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. Discontinue TREXIMET if serotonin syndrome is suspected.

5.12 Renal Toxicity and Hyperkalemia

Renal Toxicity

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

TREXIMET should be discontinued if clinical signs and symptoms consistent with renal disease develop or if systemic manifestations occur.

TREXIMET is not recommended for use in patients with severe renal impairment (creatinine clearance [CrCl] <30 mL/min) unless the benefits are expected to outweigh the risk of worsening renal function *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*. If TREXIMET is used in patients with advanced renal disease, monitor patients for signs of worsening renal function. Monitor renal function in patients with mild (CrCl = 60 to 89 mL/min) or moderate (CrCl = 30 to 59 mL/min) renal impairment, preexisting kidney disease, or dehydration.

The renal effects of TREXIMET may hasten the progression of renal dysfunction in patients with pre-existing renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating TREXIMET. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of TREXIMET *[see Drug Interactions (7)]*. Avoid the use of TREXIMET in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If TREXIMET is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with the use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.13 Anaphylactic Reactions

Anaphylactic reactions may occur in patients without known prior exposure to either component of TREXIMET. Such reactions can be life-threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens although anaphylactic reactions with naproxen have occurred in patient without known hypersensitivity to naproxen or to patients with aspirin sensitive asthma *[see Contraindications (4) and Warnings and Precautions (5.18)]*. TREXIMET should not be given to patients with the aspirin triad. This symptom complex typically occurs in patients with asthma who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs *[see Contraindications (4)]*.

TREXIMET is contraindicated in patients with a history of hypersensitivity reaction to sumatriptan, naproxen, or any other component of TREXIMET. Naproxen has been associated with anaphylactic reactions in patients without known hypersensitivity to naproxen and

in patients with aspirin-sensitive asthma *[see Contraindications (4) and Warnings and Precautions (5.18)]*. Seek emergency help if an anaphylactic reaction occurs.

5.14 Serious Skin Reactions

NSAID-containing products can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. NSAIDs can also cause fixed drug eruption (FDE). FDE may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions and to discontinue the use of TREXIMET at the first appearance of skin rash or any other sign of hypersensitivity. TREXIMET is contraindicated in patients with previous serious skin reactions to NSAIDs *[see Contraindications (4)]*.

5.15 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as TREXIMET. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue TREXIMET and evaluate the patient immediately.

5.16 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including TREXIMET, in pregnant women at about 30 weeks gestation and later. NSAIDs, including TREXIMET, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including TREXIMET, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit TREXIMET use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if TREXIMET treatment extends beyond 48 hours. Discontinue TREXIMET if oligohydramnios occurs and follow up according to clinical practice *[see Use in Specific Populations (8.1)]*.

5.17 Hematologic Toxicity

Anemia has occurred in patients receiving NSAIDs. This may be due to fluid retention, occult or gross gastrointestinal blood loss, or an incompletely described effect upon erythropoiesis. If a patient treated with TREXIMET has signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including TREXIMET, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs), and

serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding *[see Drug Interactions (7)]*.

5.18 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, TREXIMET is contraindicated in patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma *[see Contraindications (4)]*.

When TREXIMET is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.19 Seizures

Seizures have been reported following administration of sumatriptan. Some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. There are also reports in patients where no such predisposing factors are apparent. TREXIMET should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

5.20 Masking of Inflammation and Fever

The pharmacological activity of TREXIMET in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.21 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically *[see Warnings and Precautions (5.2, 5.7, 5.12)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in labeling:

- Cardiovascular Thrombotic Events *[see Warnings and Precautions (5.1)]*
- GI Bleeding, Ulceration and Perforation *[see Warnings and Precautions (5.2)]*
- Arrhythmias *[see Warnings and Precautions (5.3)]*
- Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure *[see Warnings and Precautions (5.4)]*
- Cerebrovascular Events *[see Warnings and Precautions (5.5)]*
- Other Vasospasm Reactions *[see Warnings and Precautions (5.6)]*
- Hepatotoxicity *[see Warnings and Precautions (5.7)]*
- Hypertension *[see Warnings and Precautions (5.8)]*
- Heart Failure and Edema *[see Warnings and Precautions (5.9)]*
- Medication Overuse Headache *[see Warnings and Precautions (5.10)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.11)]*
- Renal Toxicity and Hyperkalemia *[see Warnings and Precautions (5.12)]*
- Anaphylactic Reactions *[see Warnings and Precautions (5.13)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.14)]*
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) *[see Warnings and Precautions (5.15)]*
- Hematological Toxicity *[see Warnings and Precautions (5.17)]*

- Exacerbation Asthma Related to Aspirin Sensitivity *[see Warnings and Precautions (5.18)]*
- Seizures *[see Warnings and Precautions (5.19)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults

The adverse reactions reported below are specific to the clinical trials with TREXIMET 85/500 mg. See also the full prescribing information for naproxen and sumatriptan products.

Table 1 lists adverse reactions that occurred in 2 placebo-controlled clinical trials (Study 1 and 2) in adult patients who received 1 dose of study drug. Only adverse reactions that occurred at a frequency of 2% or more in any group treated with TREXIMET 85/500 mg and that occurred at a frequency greater than the placebo group are included in Table 1.

Table 1. Adverse Reactions in Pooled Placebo-Controlled Trials in Adult Patients with Migraine

Adverse Reactions	TREXIMET 85/500 mg % (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

The incidence of adverse reactions in controlled clinical trials was not affected by gender or age of the patients. There were insufficient data to assess the impact of race on the incidence of adverse reactions.

Pediatric Patients 12 to 17 Years of Age

In a placebo controlled clinical trial that evaluated pediatric patients 12 to 17 years of age who received 1 dose of TREXIMET 10/60 mg, 30/180 mg, or 85/500 mg, adverse reactions occurred in 13% of patients who received 10/60 mg, 9% of patients who received 30/180 mg, 13% who received 85/500 mg, and 8% who received placebo. No patients who received TREXIMET experienced adverse reactions leading to withdrawal from the trial. The incidence of adverse reactions in pediatric patients 12 to 17 years of age was comparable across all 3 doses compared with placebo. Table 2 lists adverse reactions that occurred in a placebo-

controlled trial in pediatric patients 12 to 17 years of age at a frequency of 2% or more with TREXIMET and were more frequent than the placebo group.

Table 2. Adverse Reactions in a Placebo-Controlled Trial in Pediatric Patients 12 to 17 Years of Age with Migraine

Adverse Reactions	**TREXIMET 10/60 mg % (n = 96)**	**TREXIMET 30/180 mg % (n = 97)**	**TREXIMET 85/500 mg % (n = 152)**	**Placebo % (n = 145)**
Vascular				
Hot flush (i.e., hot flash[es])	0	2	<1	0
Musculoskeletal				
Muscle tightness	0	0	2	0

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of NSAIDs, such as naproxen, which is a component of TREXIMET. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Appendages: exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and fixed drug eruption (FDE) *[see Warnings and Precautions (5.14)]*.

7 DRUG INTERACTIONS

7.1 Clinically Significant Drug Interactions with TREXIMET

See Table 3 for clinically significant drug interactions with NSAIDs or Sumatriptan.

Table 3. Clinically Significant Drug Interactions with Naproxen or Sumatriptan

Ergot-Containing Drugs	
Clinical Impact:	Ergot-containing drugs have been reported to cause prolonged vasospastic reactions.
Intervention:	Because these effects may be additive, coadministration of TREXIMET and ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) within 24 hours of each other is contraindicated.
Monoamine Oxidase-A Inhibitors	
Clinical Impact:	MAO-A inhibitors increase systemic exposure of orally administered sumatriptan by 7-fold.
Intervention:	The use of TREXIMET in patients receiving MAO-A inhibitors is contraindicated.
Other 5-HT_1 Agonists	
Clinical Impact:	5-HT_1 agonist drugs can cause vasospastic effects.
Intervention:	Because these effects may be additive, coadministration of TREXIMET and other 5 HT_1 agonists (e.g., triptans) within 24 hours of each other is contraindicated.

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Naproxen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of naproxen and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of TREXIMET with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding *[see Warnings and Precautions (5.17)]*.
Aspirin	
Clinical Impact:	A pharmacodynamic (PD) study has demonstrated an interaction in which lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen *[see Clinical Pharmacology (12.2)]*. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the PD study due to the longer washout period. Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.
Intervention:	Because there may be an increased risk of cardiovascular events following discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics where appropriate. Concomitant use of TREXIMET and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding *[see Warnings and Precautions (5.17)]*.
Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome	
Clinical Impact:	Cases of serotonin syndrome have been reported during coadministration of triptans and SSRIs, SNRIs, TCAs, and MAO inhibitors *[see Warnings and Precautions (5.11)]*.
Intervention:	Discontinue TREXIMET if serotonin syndrome is suspected.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-blockers	

Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of TREXIMET and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained *[see Warnings and Precautions (5.8)]*. • During concomitant use of TREXIMET and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function *[see Warnings and Precautions (5.8)]*.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of TREXIMET with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects *[see Warnings and Precautions (5.8, 5.12)]*.
Digoxin	
Clinical Impact:	The concomitant use of naproxen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of TREXIMET and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of TREXIMET and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant administration of some NSAIDs with high-dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity. Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of TREXIMET and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of NSAIDs and cyclosporine may increase cyclosporine's

	nephrotoxicity.
Intervention:	During concomitant use of TREXIMET and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of naproxen with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy *[see Warnings and Precautions (5.2)]*.
Intervention:	The concomitant use of naproxen with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of NSAIDs and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of TREXIMET and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
Probenecid	
Clinical Impact:	Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly. The clinical significance of this is unknown.
Intervention:	Reduce the frequency of administration of Treximet when given concurrently with probenecid.

7.2 Drug/Laboratory Test Interactions

Blood Tests

Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

Urine Tests

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including TREXIMET, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of TREXIMET use between about 20 and 30 weeks of gestation, and avoid TREXIMET use at about 30 weeks of gestation and later in pregnancy (*see Clinical Considerations, Data*).

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including TREXIMET, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive.

Data from a prospective pregnancy exposure registry and epidemiological studies of pregnant women have not detected an increased frequency of birth defects or a consistent pattern of birth defects among women exposed to sumatriptan compared with the general population (*see Human Data*). In animal studies, administration of sumatriptan and naproxen, alone or in combination, during pregnancy resulted in developmental toxicity (increased incidences of fetal malformations, embryofetal and pup mortality, decreased embryofetal growth) at clinically relevant doses (*see Animal Data*). Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as naproxen sodium resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The reported rate of major birth defects among deliveries to women with migraine ranged from 2.2% to 2.9% and the reported rate of miscarriage was 17%, which were similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Several studies have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including TREXIMET, can cause premature closure of the fetal ductus arteriosus (*see Data*).

Oligohydramnios/Neonatal Renal Impairment:

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If TREXIMET treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue TREXIMET and follow up according to clinical practice (*see Data*).

Labor or Delivery

There are no studies on the effects of naproxen tablets during labor or delivery. In animal studies, NSAIDS, including naproxen, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data

There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor, there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus, and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction, and abnormal prostaglandin E levels in preterm infants.

The Sumatriptan/Naratriptan/Treximet (sumatriptan and naproxen sodium) Pregnancy Registry, a population-based international prospective study, collected data for sumatriptan from January 1996 to September 2012. The Registry included only 6 pregnancy exposures to TREXIMET, with no major birth defects reported. The Registry documented outcomes of 626 infants and fetuses exposed to sumatriptan during pregnancy (528 with earliest exposure during the first trimester, 78 during the second trimester, 16 during the third trimester, and 4 unknown). The occurrence of major birth defects (excluding fetal deaths and induced abortions without reported defects and all spontaneous pregnancy losses) during first-trimester exposure to sumatriptan was 4.2% (20/478 [95% CI: 2.6% to 6.5%]) and during any trimester of exposure was 4.2% (24/576 [95% CI: 2.7% to 6.2%]). The sample size in this study had 80% power to detect at least a 1.73- to 1.91-fold increase in the rate of major malformations. The number of exposed pregnancy outcomes accumulated during the registry was insufficient to support definitive conclusions about overall malformation risk or to support making comparisons of the frequencies of specific birth defects. Of the 20 infants with reported birth defects after exposure to sumatriptan in the first trimester, 4 infants had ventricular septal defects, including one infant who was exposed to both sumatriptan and naratriptan, and 3 infants had pyloric stenosis. No other birth defect was reported for more than 2 infants in this group.

In a study using data from the Swedish Medical Birth Register, live births to women who reported using triptans or ergots during pregnancy were compared with those of women who did not. Of the 2,257 births with first-trimester exposure to sumatriptan, 107 infants were born with malformations (relative risk 0.99 [95% CI: 0.91 to 1.21]). A study using linked data from the Medical Birth Registry of Norway to the Norwegian Prescription Database compared pregnancy outcomes in women who redeemed prescriptions for triptans during pregnancy, as well as a migraine disease comparison group who redeemed prescriptions for sumatriptan before pregnancy only, compared with a population control group. Of the 415 women who redeemed prescriptions for sumatriptan during the first trimester, 15 had infants with major congenital malformations (OR 1.16 [95% CI: 0.69 to 1.94]) while for the 364 women who redeemed prescriptions for sumatriptan before, but not during, pregnancy, 20 had infants with major congenital malformations (OR 1.83 [95% CI: 1.17 to 2.88]), each compared with the population comparison group. Additional smaller observational studies evaluating use of sumatriptan during pregnancy have not suggested an increased risk of teratogenicity.

Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal Data

Oral administration of sumatriptan alone to pregnant rats during the period of organogenesis resulted in an increased incidence of fetal blood vessel (cervicothoracic and umbilical) abnormalities. The highest no-effect dose for embryofetal developmental toxicity in rats was 60 mg/kg/day, or approximately 3 times the maximum recommended human dose (MRHD) of 170 mg/day on a mg/m^2 basis.

Oral administration of sumatriptan alone to pregnant rabbits during the period of organogenesis resulted in increased incidences of embryolethality and fetal cervicothoracic vascular and skeletal abnormalities. Intravenous administration of sumatriptan to pregnant rabbits during the period of organogenesis resulted in an increased incidence of embryolethality. The highest oral and intravenous no-effect doses for developmental toxicity in rabbits were 15 (approximately 2 times the MRHD on a mg/m^2 basis) and 0.75 mg/kg/day, respectively.

Oral administration of sumatriptan combined with naproxen sodium (5/9, 25/45, or 50/90 mg/kg/day sumatriptan/naproxen sodium) or each drug alone (50/0, 0/90 mg/kg/day sumatriptan/naproxen sodium) to pregnant rabbits during the period of organogenesis resulted in increased total incidences of fetal abnormalities at all doses and increased incidences of specific malformations (cardiac interventricular septal defect in the 50/90 mg/kg/day group, fused caudal vertebrae in the 50/0 and 0/90 mg/kg/day groups) and variations (absent intermediate lobe of the lung, irregular ossification of the skull, incompletely ossified sternal centra) at the highest dose of sumatriptan and naproxen alone and in combination. A no-effect dose for developmental toxicity in rabbit was not established. The lowest effect dose of 5/9 mg/kg/day sumatriptan/naproxen sodium was associated with plasma exposures (AUC) to sumatriptan and naproxen that were less than those attained at the MRHD of 170 mg sumatriptan and 1000 mg naproxen sodium (two tablets of TREXIMET 85/500 mg in a 24-hour period).

Oral administration of sumatriptan alone to rats prior to and throughout gestation resulted in embryofetal toxicity (decreased body weight, decreased ossification, increased incidence of skeletal abnormalities). The highest no-effect dose was 50 mg/kg/day, or approximately 3 times the MRHD on a mg/m^2 basis. In offspring of pregnant rats treated orally with sumatriptan during organogenesis, there was a decrease in pup survival. The highest no-effect dose for this effect was 60 mg/kg/day, or approximately 3 times the MRHD on a mg/m^2 basis. Oral treatment of pregnant rats with sumatriptan during the latter part of gestation and throughout lactation resulted in a decrease in pup survival. The highest no-effect dose for this finding was 100 mg/kg/day, or approximately 6 times the MRHD on a mg/m^2 basis.

In reproduction studies of naproxen in rats (20 mg/kg/day), rabbits (20 mg/kg/day, and mice (170 mg/kg/day, no evidence of impaired fertility or harm to the fetus was observed. The doses tested in rats, rabbits, and mice were less (≤0.8 times) the MRHD, based on body surface area (mg/m^2) comparisons.

8.2 Lactation

Risk Summary

The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. Sumatriptan is excreted in human milk following subcutaneous administration (*see Data*). There is no information regarding sumatriptan concentrations in milk from lactating women following administration of sumatriptan tablets.

There are no data on the effects of naproxen or sumatriptan on the breastfed infant or the effects of naproxen or sumatriptan on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TREXIMET and any potential adverse effects on the breastfed infant from TREXIMET or from the underlying maternal condition.

Clinical Considerations

Infant exposure to sumatriptan can be minimized by avoiding breastfeeding for 12 hours after treatment with sumatriptan tablets.

Data

Following subcutaneous administration of a 6-mg dose of sumatriptan injection in 5 lactating volunteers, sumatriptan was present in milk.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including naproxen tablets, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including naproxen tablets, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

Safety and effectiveness of TREXIMET in pediatric patients under 12 years of age have not been established.

The safety and efficacy of TREXIMET for the acute treatment of migraine in pediatric patients 12 to 17 years of age was established in a double-blind, placebo-controlled trial *[see Adverse Reactions (6.1) and Clinical Studies (14.2)]*.

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. TREXIMET is not recommended for use in elderly patients who have decreased renal function, higher risk for unrecognized CAD, and increases in blood pressure that may be more pronounced in the elderly *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.8, 5.12) and Clinical Pharmacology (12.3)]*.

A cardiovascular evaluation is recommended for geriatric patients who have other cardiovascular risk factors (e.g., diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving TREXIMET *[see Warnings and Precautions (5.1)]*.

8.6 Renal Impairment

TREXIMET is not recommended for use in patients with creatinine clearance less than 30 mL/min. Monitor the serum creatinine or creatinine clearance in patients with mild (CrCl = 60 to 89 mL/min) or moderate (CrCL = 30 to 59 mL/min) renal impairment, preexisting kidney disease, or dehydration *[see Warnings and Precautions (5.12) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

TREXIMET is contraindicated in patients with severe hepatic impairment. For patients with mild or moderate hepatic impairment, the TREXIMET dose should be reduced. *[see Contraindications (4), Warnings and Precautions (5.7), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Patients (N = 670) have received single oral doses of 140 to 300 mg of sumatriptan without significant adverse effects. Volunteers (N = 174) have received single oral doses of 140 to 400 mg without serious adverse events.

Overdose of sumatriptan in animals has been fatal and has been heralded by convulsions, tremor, paralysis, inactivity, ptosis, erythema of the extremities, abnormal respiration, cyanosis, ataxia, mydriasis, salivation, and lacrimation.

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting and epigastric pain. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare *[see Warnings and Precautions (5.1, 5.2)]*.

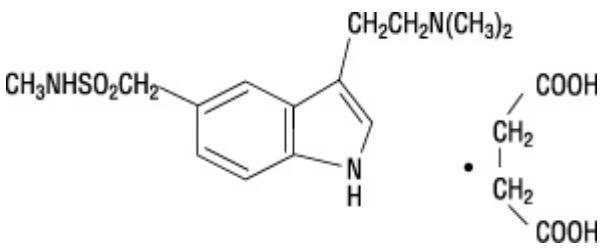
Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdosage treatment contact a poison control center (1-800-222-1222).

11 DESCRIPTION

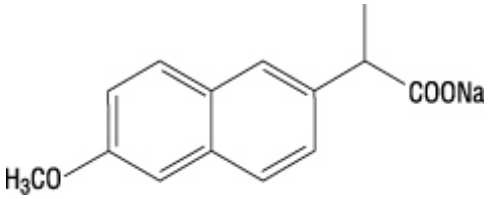
TREXIMET contains sumatriptan (as the succinate), a selective 5-hydroxytryptamine$_1$ (5-HT$_1$) receptor subtype agonist, and naproxen sodium, a member of the arylacetic acid group of NSAIDs.

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 85/500 mg 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, dibasic calcium phosphate, FD&C Blue No. 2, hypromellose, magnesium stearate, microcrystalline cellulose, povidone, sodium bicarbonate, talc, titanium dioxide, and triacetin.

Each TREXIMET 10/60 mg tablet for oral administration contains 14 mg of sumatriptan succinate equivalent to 10 mg of sumatriptan and 60 mg of naproxen sodium. Each tablet also contains the inactive ingredients croscarmellose sodium, dibasic calcium phosphate, FD&C Blue No. 2, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, sodium bicarbonate, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TREXIMET contains sumatriptan and naproxen.

Sumatriptan binds with high affinity to cloned 5-$HT_{1B/1D}$ receptors. Sumatriptan presumably exerts its therapeutic effects in the treatment of migraine headache through agonist effects at the 5-$HT_{1B/1D}$ receptors on intracranial blood vessels and sensory nerves of the trigeminal system, which result in cranial vessel constriction and inhibition of neuropeptide release.

TREXIMET has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of TREXIMET, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Naproxen is a potent inhibitor of prostaglandin synthesis *in vitro*. Naproxen concentrations reached during therapy have produced *in* vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because naproxen is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.2 Pharmacodynamics

In a healthy volunteer study, 10 days of concomitant administration of naproxen 220 mg once-daily with low-dose immediate-release aspirin (81 mg) showed an interaction with the antiplatelet activity of aspirin as measured by % serum thromboxane B_2 inhibition at

24 hours following the day 10 dose [98.7% (aspirin alone) vs 93.1% (naproxen and aspirin)]. The interaction was observed even following discontinuation of naproxen on day 11 (while aspirin dose was continued) but normalized by day 13. In the same study, the interaction was greater when naproxen was administered 30 minutes prior to aspirin [98.7% vs 87.7%] and minimal when aspirin was administered 30 minutes prior to naproxen [98.7% vs 95.4%].

Following administration of naproxen 220 mg twice-daily with low-dose immediate–release aspirin (first naproxen dose given 30 minutes prior to aspirin), the interaction was minimal at 24 h following day 10 dose [98.7% vs 95.7%]. However, the interaction was more prominent after discontinuation of naproxen (washout) on day 11 [98.7% vs 84.3%] and did not normalize completely by day 13 [98.5% vs 90.7%] *[see Drug Interactions (7.1)]*.

Blood Pressure

In a randomized, double-blind, parallel group, active control trial, TREXIMET 85/500 mg administered intermittently over 6 months did not increase blood pressure in a normotensive adult population (n = 122). However, significant elevation in blood pressure has been reported with 5-HT_1 agonists and NSAIDs in patients with and without a history of hypertension.

12.3 Pharmacokinetics

Absorption and Bioavailability

Sumatriptan, when given as TREXIMET 85/500 mg, has a mean C_{max} similar to that of sumatriptan succinate 100 mg tablets alone. The median T_{max} of sumatriptan, when given as TREXIMET 85/500 mg, was 1 hour (range: 0.3 to 4.0 hours), which is slightly different compared with sumatriptan succinate 100 mg tablets (median T_{max} of 1.5 hours). Naproxen, when given as TREXIMET 85/500 mg, has a C_{max} which is approximately 36% lower than naproxen sodium 550 mg tablets and a median T_{max} of 5 hours (range: 0.3 to 12 hours), which is approximately 4 hours later than from naproxen sodium tablets 550 mg. AUC values for sumatriptan and for naproxen are similar for TREXIMET 85/500 mg compared with sumatriptan succinate 100 mg tablets or naproxen sodium 550 mg tablets, respectively. In a crossover trial in 16 subjects, the pharmacokinetics of both components administered as TREXIMET 85/500 mg were similar during a migraine attack and during a migraine-free period.

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

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

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 *[see Dosage and Administration (2.3)]*.

Distribution

Plasma protein binding is 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated. The volume of distribution of sumatriptan is 2.7 L/kg.

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

In vitro studies with human microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme. 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

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

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.

Specific Populations

Geriatrics

The pharmacokinetics of TREXIMET in geriatric patients have not been studied. Elderly patients are more likely to have decreased hepatic function and decreased renal function *[see Specific Populations (8.5)]*.

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).

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction, which represents <1% of the total concentration, increased in the elderly (range of unbound trough naproxen from 0.12% to 0.19% in elderly subjects versus 0.05% to 0.075% in younger subjects).

Pediatrics

A pharmacokinetic study compared 3 doses of TREXIMET in pediatric patients 12 to 17 years of age (n=24) with adults (n=26). The AUC and C_{max} of sumatriptan were 50-60% higher following a single dose of TREXIMET 10/60 mg in pediatric patients 12 to 17 years of age (n=7) compared with adult subjects (n=8), and were 6-26% higher following a single dose of TREXIMET 30/180 mg or 85/500 mg in pediatrics than adults. Naproxen pharmacokinetic parameters were similar between pediatrics and adults.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of TREXIMET has not been studied. 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 *[see Warnings and Precautions (5.12), Use in Specific Populations (8.6)]*.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of TREXIMET has not been studied. In a study in patients with moderate hepatic impairment (n = 8) matched for sex, age, and weight with healthy subjects (n = 8), patients with hepatic impairment had an approximately 70% increase in AUC and C_{max} of sumatriptan and a T_{max} 40 minutes earlier compared to healthy subjects. The pharmacokinetics of sumatriptan in patients with severe hepatic impairment has not been studied.

Gender

In a pooled analysis of 5 pharmacokinetic trials, there was no effect of gender on the systemic exposure of TREXIMET.

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 white (n = 38) healthy male subjects.

Drug Interaction Studies

Aspirin

When naproxen was administered with aspirin (>1 gram/day), the protein binding of naproxen was reduced, although the clearance of free naproxen was not altered. See Table 3 for clinically significant drug interactions of naproxen, an NSAID, with aspirin *[see Drug Interactions (7)]*.

Propranolol

Propranolol 80 mg given twice daily had no significant effect on sumatriptan pharmacokinetics. See Table 3 for clinically significant drug interactions of propranolol, a beta-blocker, with TREXIMET *[see Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of TREXIMET has not been studied.

In carcinogenicity studies in mouse and rat, sumatriptan was administered orally for 78 and 104 weeks, respectively, at doses up to 160 mg/kg/day. The highest doses tested are approximately 5 (mouse) and 9 (rat) times the maximum human daily dose (MHDD) of 170 mg sumatriptan on a mg/m^2 basis (two tablets of TREXIMET 85/500 mg in a 24-hour period).

The carcinogenic potential of naproxen was evaluated in a 2-year oral carcinogenicity study in rats at doses of 8, 16, and 24 mg/kg/day and in another 2-year oral carcinogenicity study in rats at a dose of 8 mg/kg/day. No evidence of tumorigenicity was found in either study. The highest dose tested is less than the MHDD (1000 mg) of naproxen, on a mg/m^2 basis.

Mutagenesis

Sumatriptan and naproxen sodium tested alone and in combination were negative in an in vitro bacterial reverse mutation assay, and in an in vivo micronucleus assay in mice.

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

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

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

In previous studies, sumatriptan alone was negative in in vitro (bacterial reverse mutation [Ames], gene cell mutation in Chinese hamster V79/HGPRT, chromosomal aberration in human lymphocytes) and in vivo (rat micronucleus) assays.

Impairment of Fertility

The effect of TREXIMET on fertility in animals has not been studied.

When sumatriptan (5, 50, 500 mg/kg/day) was administered orally to male and female rats prior to and throughout the mating period, there was a drug-related decrease in fertility secondary to a decrease in mating in animals treated with doses greater than 5 mg/kg/day (less than the MHDD of 170 mg on a mg/m^2 basis). It is not clear whether this finding was due to an effect on males or females or both.

13.2 Animal Toxicology and/or Pharmacology

Corneal Opacities

Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established. The lowest dose tested is less than the MHDD (170 mg) of sumatriptan on a mg/m^2 basis.

14 CLINICAL STUDIES

14.1 Adults

The efficacy of TREXIMET in the acute treatment of migraine with or without aura in adults was demonstrated in 2 randomized, double-blind, multicenter, parallel-group trials utilizing placebo and each individual active component of TREXIMET 85/500 mg (sumatriptan and naproxen sodium) as comparison treatments (Study 1 and Study 2). Patients enrolled in these 2 trials were predominately female (87%) and white (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 Study 1 and 2 are summarized in Table 4. In both trials, the percentage of patients achieving headache pain relief 2 hours after treatment was significantly greater among patients receiving TREXIMET 85/500 mg (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 85/500 mg (25% and 23%) compared with those who received placebo (8% and 7%) or either sumatriptan (16% and 14%) or naproxen sodium (10%) alone.

Table 4. Percentage of Adult Patients with 2-Hour Pain Relief and Sustained Pain Free Following Treatment[a]

	TREXIMET 85/500 mg	Sumatriptan 85 mg	Naproxen Sodium 500 mg	Placebo
2-Hour Pain Relief				
Study 1	65%[b] n = 364	55% n = 361	44% n = 356	28% n = 360
Study 2	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

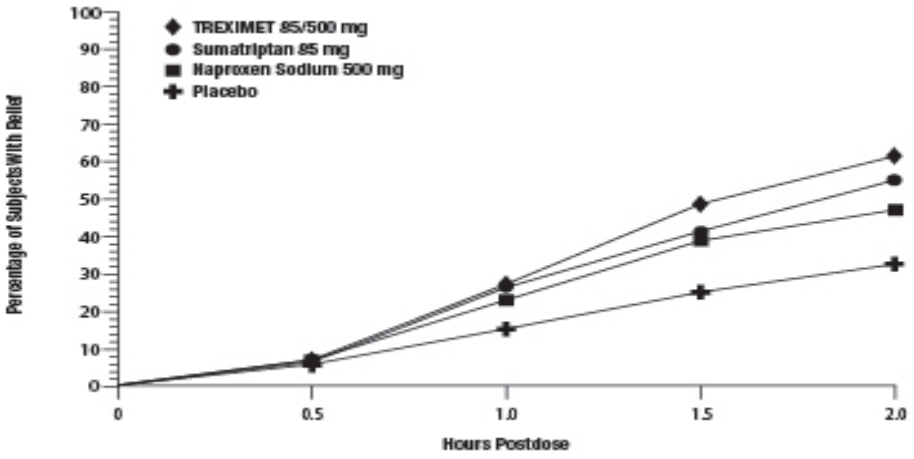
[a] *P* values provided only for prespecified comparisons.

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

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

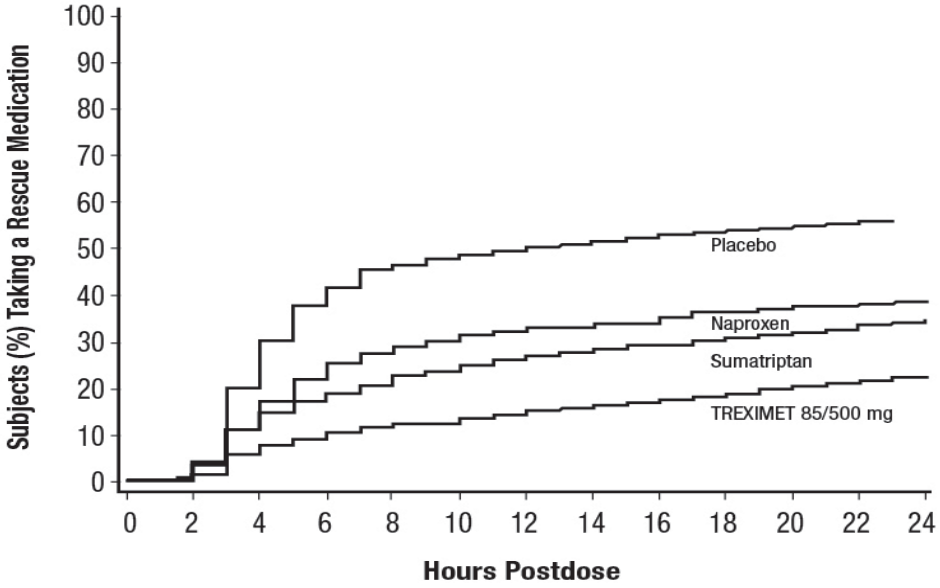
The percentage of patients achieving initial headache pain relief within 2 hours following treatment with TREXIMET 85/500 mg is shown in Figure 1.

Figure 1. Percentage of Adult Patients with Initial Headache Pain Relief within 2 Hours



Compared with placebo, there was a decreased incidence of photophobia, phonophobia, and nausea 2 hours after the administration of TREXIMET 85/500 mg. The estimated probability of taking a rescue medication over the first 24 hours is shown in Figure 2.

Figure 2. Estimated Probability of Adults Taking a Rescue Medication over the 24 Hours following the First Dose[a]



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

TREXIMET 85/500 mg was more effective than placebo regardless of the presence of aura; duration of headache prior to treatment; gender, age, or weight of the subject; or concomitant use of oral contraceptives or common migraine prophylactic drugs (e.g., beta-blockers, anti-epileptic drugs, tricyclic antidepressants).

14.2 Pediatric Patients 12 to 17 Years of Age

The efficacy of TREXIMET in the acute treatment of migraine with or without aura in pediatric patients 12 to 17 years of age was demonstrated in a randomized, double-blind, multicenter, parallel-group, placebo-controlled, multicenter trial comparing 3 doses of TREXIMET and placebo (Study 3). Patients enrolled in this trial were mostly female (59%) and white (81%), with a mean age of 15 years.

Patients were required to have at least a 6-month history of migraine attacks with or without aura usually lasting 3 hours or more when untreated. Following a single-blind, placebo run-in phase, placebo nonresponders were randomized to receive a single dose of either TREXIMET 10/60 mg, 30/180 mg, 85/500 mg, or placebo. Patients were instructed to treat a single migraine attack with headache pain of moderate to severe intensity. No rescue medication was allowed within 2 hours postdose. Patients evaluated their headache pain 2 hours after taking 1 dose of study medication. Two-hour pain free was defined as a reduction in headache severity from moderate or severe pain to no pain at 2 hours postdose.

Results are summarized in Table 5. The percentage of patients who were pain free at 2 hours postdose was significantly greater among patients who received any of the 3 doses of TREXIMET compared with placebo.

Table 5. Percentage of Pediatric Patients 12 to 17 Years of Age with 2-Hour Pain-Free Response Following Treatment in Study 3[a]

Endpoint	**TREXIMET 10/60 mg** (n = 96)	**TREXIMET 30/180 mg** (n = 97)	**TREXIMET 85/500 mg** (n = 152)	**Placebo** (n = 145)
2-Hour Pain Free	29%[b]	27%[b]	24%[b]	10%

[a]*P* values provided only for prespecified comparisons.
[b]*P*<0.01 versus placebo.

The percentage of pediatric patients who remained pain free without use of other medications 2 through 24 hours postdose was significantly greater after administration of a single dose of TREXIMET 85/500 mg compared with placebo. A greater percentage of pediatric patients who received a single dose of 10/60 mg or 30/180 mg remained pain free 2 through 24 hours postdose compared with placebo.

Compared with placebo, the incidence of photophobia and phonophobia was significantly decreased 2 hours after the administration of a single dose of 85/500 mg, whereas, the incidence of nausea was comparable. There was a decreased incidence of photophobia, phonophobia, and nausea 2 hours after single-dose administration of 10/60 mg or 30/180 mg compared with placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

TREXIMET 85/500 mg contains 119 mg of sumatriptan succinate equivalent to 85 mg of sumatriptan and 500 mg of naproxen sodium and is supplied as blue film-coated tablets debossed on one side with *TREXIMET* in bottles of 9 tablets with desiccant (NDC 42847-850-09).

TREXIMET 10/60 mg contains 14 mg of sumatriptan succinate equivalent to 10 mg of sumatriptan and 60 mg of naproxen sodium and is supplied as light-blue film-coated tablets debossed on one side with *TREXIMET* and the other side with *10-60* in bottles of 9 tablets with desiccant (NDC 42847-860-09).

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with TREXIMET and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events, Prinzmetal's Angina, Other Vasospasm-Related Events, Arrhythmias and Cerebrovascular Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic effects such as myocardial infarction or stroke, which may result in hospitalization and even death. Although serious cardiovascular events can occur without warning symptoms, patients should be alert for signs and symptoms of chest pain, shortness of breath, weakness, irregular heartbeat, significant rise in blood pressure, weakness and slurring of speech, and should be advised to report any of these symptoms to their health care provider immediately. Apprise patients of the importance of this follow-up *[see Warnings and Precautions (5.1, 5.3, 5.5, 5.6, 5.8)]*.

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop TREXIMET and seek immediate medical therapy *[see Warnings and Precautions (5.7)]*.

Anaphylactic Reactions

Inform patients that anaphylactic reactions have occurred in patients receiving the components of TREXIMET. Such reactions can be life-threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help *[see Contraindications (4), Warnings and Precautions (5.13)]*.

Serious Skin Reactions, including DRESS

Inform patients that TREXIMET, like other NSAID-containing products, may increase the risk of serious skin side effects such as exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching and should ask for medical advice when observing any indicative signs or symptoms. Advise patients to stop taking TREXIMET immediately if they develop any type of rash or fever and contact their healthcare providers as soon as possible *[see Warnings and Precautions (5.14, 5.15)]*.

Fetal Toxicity

Inform pregnant women to avoid use of TREXIMET and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with TREXIMET is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours *[see Warnings and Precautions (5.16), Use in Specific Populations (8.1)]*.

Lactation

Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed *[see Use in Specific Populations (8.2)]*.

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including TREXIMET, may be associated with a reversible delay in ovulation *[see Use in Specific Populations (8.3)]*.

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur *[see Warnings and Precautions (5.9)]*.

Concomitant Use with Other Triptans or Ergot Medications

Inform patients that use of TREXIMET within 24 hours of another triptan or an ergot-type medication (including dihydroergotamine or methysergide) is contraindicated *[see Contraindications (4), Drug Interactions (7.1)]*.

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with the use of TREXIMET or other triptans, particularly during concomitant use with SSRIs, SNRIs, TCAs, and MAO inhibitors *[see Warnings and Precautions (5.11), Drug Interactions (7.1)]*.

Medication Overuse Headache

Inform patients that use of acute migraine drugs for 10 or more days per month may lead to an exacerbation of headache and encourage patients to record headache frequency and drug use (e.g., by keeping a headache diary) *[see Warnings and Precautions (5.10)]*.

Ability to Perform Complex Tasks

Treatment with TREXIMET may cause somnolence and dizziness; instruct patients to evaluate their ability to perform complex tasks after administration of TREXIMET *[see Adverse Reactions (6.1)]*.

Asthma

Advise patients with preexisting asthma to seek immediate medical attention if their asthma worsens after taking TREXIMET. Patients with a history of aspirin-sensitive asthma should not take TREXIMET *[see Contraindications (4), Warnings and Precautions (5.18)]*.

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of TREXIMET with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy *[see Warnings and Precautions (5.2) and Drug Interactions (7)]*. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDS and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with TREXIMET until they talk to their healthcare provider *[see Drug Interactions (7)]*.

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MEDICATION GUIDE

TREXIMET® [trex' i-met] Tablets

(sumatriptan and naproxen sodium)

Read this Medication Guide before you start taking TREXIMET and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or treatment.

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

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

- This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

Do not take TREXIMET right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

Avoid taking TREXIMET after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

Stop taking TREXIMET and get emergency help right away if you have any of the following symptoms of a heart attack or stroke:

- discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw, or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded
- weakness in one part or on one side of your body
- slurred speech

TREXIMET is not for people with risk factors for heart disease unless a heart exam is done and shows no problem. You have a higher risk for heart disease if you:

- have high blood pressure
- smoke
- have diabetes
- have high cholesterol levels
- are overweight
- have a family history of heart disease

TREXIMET can cause ulcers and bleeding in the stomach and intestines at any time during your treatment. Ulcers and bleeding can happen without warning symptoms and may cause death.

Your chance of getting an ulcer or bleeding increases with:

- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- the use of medicines called "corticosteroids," "anticoagulants," and antidepressant medicines called "SSRIs" or "SNRIs"
- more frequent use
- drinking alcohol
- having poor health
- advanced liver disease
- bleeding problems
- longer use
- smoking
- older age

TREXIMET may cause serious allergic reactions or serious skin reactions that can be life-threatening. Stop taking TREXIMET and get emergency help right away if you develop:

- sudden wheezing
- rash
- problems breathing or swallowing
- blisters or bleeding of your lips, eye lids, mouth, nose, or genitals
- swelling of your lips, tongue, throat or body
- fainting
- reddening of your skin with blisters or peeling

TREXIMET should only be used exactly as prescribed, at the lowest dose possible for your treatment, and for the shortest time needed.

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

What is TREXIMET?

TREXIMET is a prescription medicine that contains sumatriptan and naproxen sodium (an NSAID). TREXIMET is used to treat acute migraine headaches with or without aura in patients 12 years of age and older.

TREXIMET is not used to treat other types of headaches such as hemiplegic (that make you unable to move on one side of your body) or basilar (rare form of migraine with aura) migraines.

TREXIMET is not used to prevent or decrease the number of migraine headaches you have.

It is not known if TREXIMET is safe and effective to treat cluster headaches.

Who should not take TREXIMET?

Do not take TREXIMET if you have:

- heart problems, history of heart problems, or right before or after heart bypass surgery
- had a stroke, transient ischemic attack (TIAs), or problems with your blood circulation
- hemiplegic migraines or basilar migraines. If you are not sure if you have these types of migraines, ask your healthcare provider.
- narrowing of blood vessels to your legs and arms (peripheral vascular disease), stomach (ischemic bowel disease), or kidneys
- uncontrolled high blood pressure
- taken any medicines in the last 24 hours that are called 5-HT_1 agonists that are triptans or contain ergotamine. Ask your healthcare provider for a list of these medicines if you are not sure.
- taken an antidepressant medicine called a monoamine oxidase (MAO) inhibitor within the last 2 weeks. Ask your healthcare provider for a list if you are not sure.
- had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- an allergy to sumatriptan, naproxen, or any of the ingredients in TREXIMET. See “What are the ingredients in TREXIMET?” below for a complete list of ingredients.
- liver problems

What should I tell my healthcare provider before taking TREXIMET?

Before you take TREXIMET, tell your healthcare provider about all of your medical conditions, including if you:

- have high blood pressure
- have asthma
- have high cholesterol
- have diabetes
- smoke
- are overweight
- have heart problems or a family history of heart problems or stroke
- have kidney problems
- have liver problems
- have had epilepsy or seizures
- are not using effective birth control
- are pregnant, think you might be pregnant, or are trying to become pregnant. Taking NSAIDs, including TREXIMET, at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**
- are breastfeeding or plan to breastfeed. The components of TREXIMET pass into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you take TREXIMET.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

TREXIMET and certain other medicines can affect each other, causing serious side effects.

How should I take TREXIMET?

- Certain people should take their first dose of TREXIMET in their healthcare provider’s office or in another medical setting. Ask your healthcare provider if you should take your first dose in a medical setting.
- Take TREXIMET exactly as your healthcare provider tells you to take it.
- Take TREXIMET tablets whole with water or other liquids.
- TREXIMET can be taken with or without food.
- If you do not get any relief after your first dose, do not take a second dose without first talking with your healthcare provider.
- If your headache comes back or you only get some relief from your headache:
  - For adults: a second dose may be taken 2 hours after the first dose. Do not take more than 2 doses of TREXIMET 85/500 mg in a 24-hour period.
  - For children 12 to 17 years of age: it is not known if taking more than 1 dose of TREXIMET in 24 hours is safe and effective. Talk to your healthcare provider about what to do if your headache does not go away or comes back.
- If you take too much TREXIMET, call your healthcare provider or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you take TREXIMET so you can talk with your healthcare provider about how TREXIMET is working for you.

What should I avoid while taking TREXIMET?

TREXIMET can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not drive a car, use machinery, or do anything where you need to be alert.

What are the possible side effects of TREXIMET?

TREXIMET may cause serious side effects. See "What is the most important information I should know about TREXIMET?"

These serious side effects include:

- changes in color or sensation in your fingers and toes (Raynaud's syndrome)
- new or worse high blood pressure
- heart failure from body swelling (fluid retention)
- kidney problems including kidney failure
- low red blood cells (anemia)
- liver problems including liver failure
- asthma attacks in people who have asthma
- stomach and intestinal problems (gastrointestinal and colonic ischemic events). Symptoms of gastrointestinal and colonic ischemic events include:
    - sudden or severe stomach pain
    - weight loss
    - constipation or diarrhea
    - fever
    - stomach pain after meals
    - nausea or vomiting
    - bloody diarrhea
- problems with blood circulation to your legs and feet (peripheral vascular ischemia). Symptoms of peripheral vascular ischemia include:
    - cramping and pain in your legs or hips
    - feeling of heaviness or tightness in your leg muscles
    - burning or aching pain in your feet or toes while resting
    - numbness, tingling, or weakness in your legs
    - cold feeling or color changes in 1 or both legs or feet
- medication overuse headaches. Some people who use too many TREXIMET tablets may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with TREXIMET.
- serotonin syndrome. Serotonin syndrome is a rare but serious problem that can happen in people using TREXIMET, especially if TREXIMET is used with antidepressant medicines called SSRIs or SNRIs.
  Stop taking TREXIMET and call your healthcare provider right away if you have any of the following symptoms of serotonin syndrome:
    - changes in blood pressure
    - tight muscles
    - mental changes such as seeing things that are not there (hallucinations), agitation, or coma
    - fast heartbeat
    - high body temperature
    - trouble walking
- seizures. Seizures have happened in people taking sumatriptan, one of the ingredients in TREXIMET, who have never had seizures before. Talk with your healthcare provider about your chance of having seizures while you take TREXIMET.

The most common side effects of TREXIMET include:

- dizziness
- pain, discomfort, or stiffness in your neck, throat, jaw, or chest
- tingling or numbness in your fingers or toes
- dry mouth
- heartbeat problems
- feeling weak, drowsy, or tired
- nausea
- heartburn
- feeling hot
- muscle tightness

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

- nausea that seems out of proportion to your migraine
- vomit blood
- yellow skin or eyes
- more tired or weaker than usual
- itching
- swelling of the arms, legs, hands, and feet
- sudden or severe stomach pain
- blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- flu-like symptoms
- diarrhea
- tenderness in your upper right side

Tell your healthcare provider if you have any side effects that bother you or do not go away.

These are not all of the side effects of TREXIMET. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TREXIMET?

Store TREXIMET at room temperature between 68°F to 77°F (20°C to 25°C).

Keep TREXIMET and all medicines out of the reach of children.

General information about the safe and effective use of TREXIMET

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TREXIMET for a condition for which it was not prescribed. Do not give TREXIMET to other people, even if they have the same problem you have. It may harm them.

This Medication Guide summarizes the most important information about TREXIMET. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about TREXIMET that is written for healthcare professionals.

For more information call 1-800-793-2145 or visit www.TREXIMET.com.

What are the ingredients in TREXIMET?

Active ingredients: sumatriptan succinate and naproxen sodium.

Inactive ingredients in all strengths: croscarmellose sodium, dibasic calcium phosphate, FD&C Blue No. 2, magnesium stearate, microcrystalline cellulose, povidone, sodium bicarbonate, talc, and titanium dioxide.
85/500-mg tablets also contain: hypromellose and triacetin.
10/60-mg tablets also contain: polyethylene glycol and polyvinyl alcohol.

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This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 02/2024