**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: CARDIOVASCULAR AND GASTROINTESTINAL RISKS**

***See full prescribing information for complete boxed warning.***

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (5.2)**

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

| | |
|---|---|
| Indications and Usage (1) | 05/2015 |
| Dosage and Administration (2.2) | 05/2015 |

**---------- 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)
- History of coronary artery bypass graft 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)
- Asthma, rhinitis, and nasal polyps syndrome induced by aspirin or other NSAID/analgesic drugs. (4)
- Hypersensitivity to sumatriptan, naproxen, or any other component of TREXIMET (angioedema and anaphylaxis seen). (4)
- Third trimester of pregnancy. (4)
- Severe hepatic impairment. (4)

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

- Myocardial ischemia/infarction, stroke, Prinzmetal's angina: Perform cardiac evaluation in patients with cardiovascular risk factors. (5.1)
- Arrhythmias: Discontinue TREXIMET if occurs. (5.3)
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness: Generally not associated with myocardial ischemia; evaluate for coronary artery disease in patients at high risk. (5.4)
- Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Discontinue TREXIMET if occurs. (5.5)
- Gastrointestinal ischemic reactions and peripheral vasospastic reactions: Discontinue TREXIMET if occurs. (5.6)
- Hypertension: Monitor blood pressure. (5.7)
- Heart failure and edema: Use with caution in patients with fluid retention or heart failure. (5.8)
- Medication overuse headache: Detoxification may be necessary (5.9)
- Serotonin syndrome: Discontinue TREXIMET if occurs. (5.10)
- Renal papillary necrosis and other renal injury with long-term use: Discontinue TREXIMET if occurs. (5.11)
- Anaphylactic reactions: TREXIMET should not be given to patients with the aspirin triad. (5.12)
- Serious skin reactions: Discontinue TREXIMET at first sign of rash. (5.13)
- Elevated liver enzymes and severe hepatic reactions: Discontinue use immediately if abnormal liver enzymes persist or worsen. (5.15)

**---------- 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 Pernix Therapeutics at 1-800-793-2145 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**---------- DRUG INTERACTIONS----------**

- Methotrexate: Increases methotrexate plasma levels. (7.4)
- Aspirin: Use not recommended. (7.5)
- Angiotensin-converting enzyme inhibitors, diuretics, beta-blockers: May reduce antihypertensive effects. (7.7)
- Lithium: Increases lithium plasma levels. (7.9)
- Warfarin: Higher risk of serious gastrointestinal bleeding. (7.12)

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

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Severe Renal impairment: Not recommended in patients with creatinine clearance <30 mL/min. (8.6)

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

**Revised: 05/2015**

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**FULL PRESCRIBING INFORMATION**

**WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISKS**

- **Cardiovascular Risk: Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk *[see Warnings and Precautions (5.1)]*.**
- **Gastrointestinal Risk: NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events *[see Warnings 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.

### 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.

### 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)]*.

### 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)]*.
- History 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 (5.7)]*.
- 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 (7.1, 7.3)]*.
- Concurrent administration of a monoamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor *[see Drug Interactions (7.2), Clinical Pharmacology (12.3)]*.
- Asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs *[see Warnings and Precautions (5.12, 5.13, 5.17)]*.
- Hypersensitivity to sumatriptan, naproxen, or any other component of TREXIMET. Reactions have included angioedema and anaphylaxis *[see Warnings and Precautions (5.12)]*.
- Third trimester of pregnancy *[see Warnings and Precautions (5.14), Use in Specific Populations (8.1)]*.
- Severe hepatic impairment *[see Warnings and Precautions (5.15), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Myocardial Ischemia, Myocardial Infarction, Stroke, Prinzmetal's Angina

The use of TREXIMET is contraindicated in patients with ischemic or vasospastic coronary artery disease (CAD) or with a history of 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 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 thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known cardiovascular disease or risk factors for cardiovascular

disease may be at greater risk. To minimize the potential risk for an adverse cardiovascular event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious gastrointestinal events *[see Warnings and Precautions (5.2)]*.

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.

Premarketing Experience with TREXIMET

Among 3,302 adult patients with migraine who received TREXIMET in premarketing controlled and uncontrolled clinical trials, a 47-year-old female with cardiac risk factors in an open-label 12-month safety trial experienced signs and symptoms of acute coronary syndrome approximately 2 hours after receiving TREXIMET.

**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.

TREXIMET should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. 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 concomitant use of oral corticosteroids or anticoagulants or antiplatelets (including low-dose aspirin), longer duration of NSAID therapy, 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.

To minimize the potential risk for an adverse gastrointestinal event in NSAID-treated patients, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of gastrointestinal

ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal adverse event is suspected. This should include discontinuation of the NSAID until a serious gastrointestinal adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

### 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 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 patients without a history of hypertension.

NSAIDs, including naproxen, a component of TREXIMET, can 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 thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs.

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

### 5.8 Heart Failure and Edema

Fluid retention, edema, and peripheral edema have been observed in some patients taking NSAIDs. 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. TREXIMET should be used with caution in patients with fluid retention or heart failure.

### 5.9 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.

### 5.10 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 Drug Interactions (7.6)]*. 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.

### 5.11 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, hypovolemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and angiotensin-converting enzyme (ACE) inhibitors, 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) *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*. 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.

### 5.12 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. TREXIMET is contraindicated in patients with a history of hypersensitivity reaction to sumatriptan, naproxen, or any other component of TREXIMET *[see Contraindications (4)]*.

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)]*.

**5.13 Serious Skin Reactions**

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

**5.14 Pregnancy**

TREXIMET should not be used during the third trimester of pregnancy because NSAID-containing products have been shown to cause premature closure of the ductus arteriosus *[see Contraindications (4), Use in Specific Populations (8.1)]*.

**5.15 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, cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis, and hepatic failure, some of them with fatal outcomes, 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.

**5.16 Hematologic Toxicity**

Anemia is sometimes seen in patients receiving NSAIDs. This may be due to fluid retention, occult or gross gastrointestinal blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including TREXIMET, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

NSAID-containing products inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving TREXIMET who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

**5.17 Exacerbation of Asthma Related to Aspirin Sensitivity**

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm that can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, TREXIMET should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma *[see Contraindications (4), Warnings and Precautions (5.12)]*.

### 5.18 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.

## 6 ADVERSE REACTIONS

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

- Myocardial Ischemia/Infarction, Stroke, Prinzmetal's Angina *[see Warnings and Precautions (5.1)]*
- Gastrointestinal effects *[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)*
- Increase in blood pressure *[see Warnings and Precautions (5.7)]*
- Congestive heart failure and edema *[see Warnings and Precautions (5.8)]*
- Medication overuse headache *[see Warnings and Precautions (5.9)*
- Serotonin syndrome *[see Warnings and Precautions (5.10)]*
- Renal Toxicity *[see Warnings and Precautions (5.11)]*
- Anaphylactic reactions *[see Contraindications (4), Warnings and Precautions (5.12)]*
- Serious skin reactions *[see Warnings and Precautions (5.13)]*
- Hepatotoxicity *[see Warnings and Precautions (5.15)]*
- Hematological toxicity *[see Warnings and Precautions (5.16)]*
- Exacerbation Asthma Related to Aspirin Sensitivity *[see Warnings and Precautions (5.17)]*
- Seizures *[see Warnings and Precautions (5.18)]*

### 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 |

## 7 DRUG INTERACTIONS

### 7.1 Ergot-Containing Drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and TREXIMET within 24 hours of each other is contraindicated.

### 7.2 Monoamine Oxidase-A Inhibitors

MAO-A inhibitors increase systemic exposure of orally administered sumatriptan by 7-fold. Therefore, the use of TREXIMET in patients receiving MAO-A inhibitors is contraindicated.

### 7.3 Other 5-$HT_1$ Agonists

Because their vasospastic effects may be additive, coadministration of TREXIMET and other 5-$HT_1$ agonists (e.g., triptans) within 24 hours of each other is contraindicated.

### 7.4 Methotrexate

Naproxen sodium and other NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly increasing the toxicity of methotrexate. 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. During concomitant use of TREXIMET and methotrexate, monitor patients for methotrexate toxicity.

### 7.5 Aspirin

When naproxen is administered with aspirin (>1 gram/day), its protein binding is reduced, although the clearance of free naproxen is not altered. Concomitant administration of TREXIMET and aspirin is not generally recommended because of the increased risk of bleeding *[see Warnings and Precautions (5.2)]*.

### 7.6 Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of serotonin syndrome have been reported during coadministration of triptans and SSRIs, SNRIs, TCAs, and MAO inhibitors *[see Warnings and Precautions (5.10)]*.

### 7.7 Angiotensin-Converting Enzyme Inhibitors

NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors. The use of TREXIMET in patients who are receiving ACE inhibitors may potentiate renal disease states *[see Warnings and Precautions (5.11)]*. Monitor for signs of worsening renal function during concomitant use of TREXIMET and ACE-inhibitors in patients who are elderly, volume-depleted, or have impaired renal function.

### 7.8 Diuretics

Clinical trials, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant use of TREXIMET, observe patients for signs of renal failure, in addition to assuring diuretic efficacy *[see Warnings and Precautions (5.11)]*.

### 7.9 Lithium

NSAIDs elevated plasma lithium levels and a reduced renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance was decreased by approximately 20%. These effects have been attributed to NSAID inhibition of renal prostaglandin synthesis. During concomitant use of TREXIMET and lithium, monitor patients for signs of lithium toxicity.

### 7.10 Probenecid

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

### 7.11 Propranolol and Other Beta-Blockers

Propranolol 80 mg given twice daily had no significant effect on sumatriptan pharmacokinetics. Naproxen and other NSAIDs can reduce the antihypertensive effect of propranolol and other beta-blockers.

### 7.12 Warfarin

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

### 7.13 Drug/Laboratory Test Interactions

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

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

Pregnancy Category C during the first two trimesters of pregnancy; Category X during the third trimester of pregnancy. There are no adequate and well-controlled studies in pregnant women. TREXIMET (sumatriptan and naproxen) should be used during the first and second trimester of pregnancy only if the potential benefit justifies the potential risk to the fetus. TREXIMET should not be used during the third trimester of pregnancy because inhibitors of prostaglandin synthesis (including naproxen) are known to cause premature closure of the ductus arteriosus in humans. 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.

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 or 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 rabbits was not established. The lowest effect dose was 5/9 mg/kg/day sumatriptan/naproxen sodium, which was associated with plasma exposures (AUC) to sumatriptan and naproxen that were less than those attained at the maximum human daily dose (MHDD) of 170 mg sumatriptan and 1000 mg naproxen sodium (two tablets of TREXIMET 85/500 mg in a 24-hour period).

In previous developmental toxicity studies of sumatriptan, oral administration to pregnant rats during the period of organogenesis resulted in an increased incidence of fetal blood vessel abnormalities and decreased pup survival at doses of 250 mg/kg/day or higher.

The highest no-effect dose was 60 mg/kg/day, which is approximately 3 times the MHDD of 170 mg sumatriptan on a mg/m$^2$ basis. Oral administration of sumatriptan to pregnant rabbits during the period of organogenesis resulted in increased incidences of vascular and skeletal abnormalities at a dose of 50 mg/kg/day and embryolethality at 100 mg/kg/day. The highest no-effect dose of sumatriptan for developmental toxicity in rabbits was 15 mg/kg/day, or approximately 2 times the MHDD of 170 mg sumatriptan on a mg/m$^2$ basis.

### 8.2 Labor and Delivery

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

### 8.3 Nursing Mothers

Both active components of TREXIMET, sumatriptan and naproxen, have been reported to be secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from TREXIMET, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 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

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, 5.7, 5.11), 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 (5.11), 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 (5.15), 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.

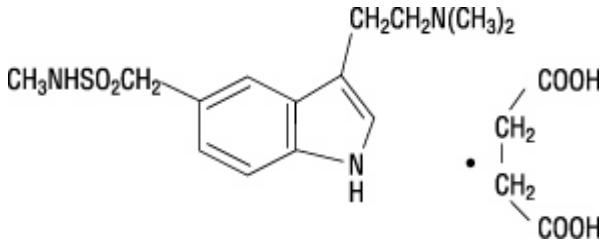
In addition to the adverse events already described, significant naproxen overdosage may be characterized by lethargy, epigastric pain, abdominal discomfort, transient alterations in liver function, hypoprothrombinemia, metabolic acidosis, apnea, disorientation, or vomiting. Acute renal failure, respiratory depression, and coma may occur, but are rare.

Patients should be managed by symptomatic and supportive care. There are no specific antidotes. 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, or hemoperfusion may not be useful due to high protein binding.

## 11 DESCRIPTION

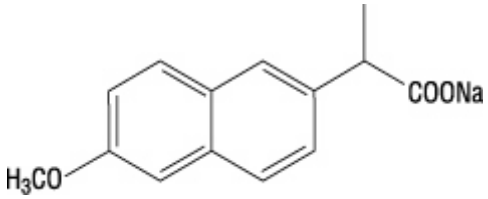
TREXIMET contains sumatriptan (as the succinate), a selective 5-hydroxytryptamine$_1$ (5-HT$_1$) receptor subtype agonist, and naproxen sodium, a member of the arylacetic acid group of NSAIDs.

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, dextrose monohydrate, dibasic calcium phosphate, FD&C Blue No. 2, lecithin, magnesium stearate, maltodextrin, microcrystalline cellulose, povidone, sodium bicarbonate, sodium carboxymethylcellulose, talc, and titanium dioxide.

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.

Naproxen is an NSAID with analgesic and antipyretic properties. The mechanism of action of naproxen, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

### 12.2 Pharmacodynamics

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 Cmax 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 (5.11), 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.

## 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 3. 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 3. 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 |

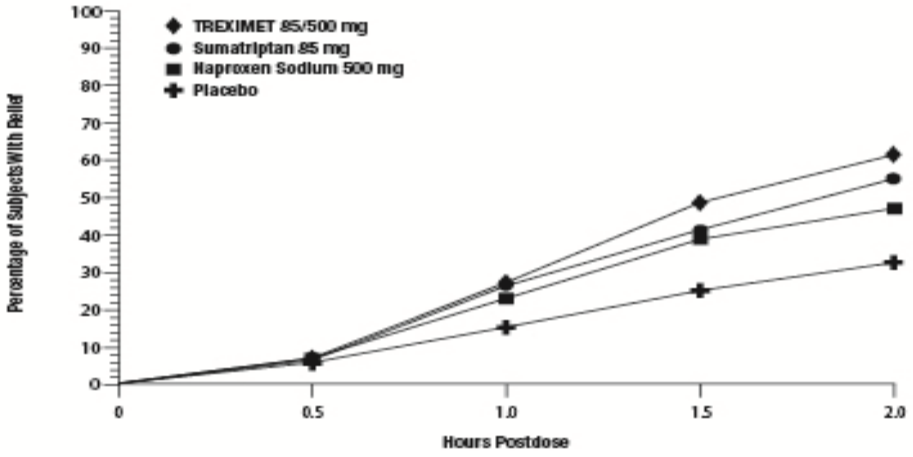
[a] *P* values provided only for prespecified comparisons.

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

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

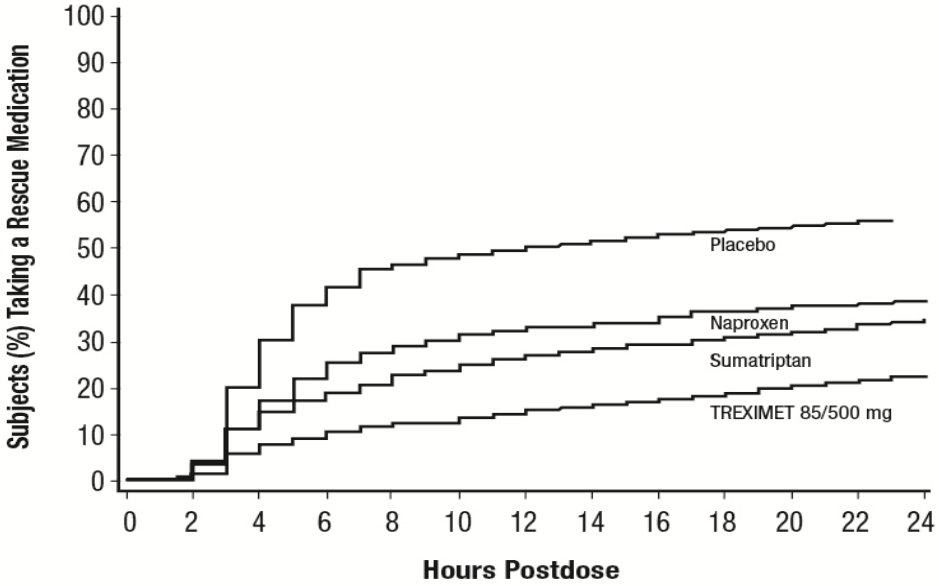
The percentage of patients achieving initial headache pain relief within 2 hours following treatment with TREXIMET 85/500 mg is shown in Figure 1.

**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 4. 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 4. 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 65224-850-09).

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 65224-860-09).

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).

Risk of Myocardial Ischemia and/or Infarction, Prinzmetal's Angina, Other Vasospasm-Related Events, Arrhythmias, and Cerebrovascular Events

Inform patients that TREXIMET may cause serious cardiovascular side 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 the signs and symptoms of chest pain, shortness of breath, irregular heartbeat, significant rise in blood pressure, weakness, and slurring of speech, and should ask for medical advice if any indicative sign or symptoms are observed. Apprise patients of the importance of this follow-up *[see Warnings and Precautions (5.1, 5.3, 5.5, 5.6, 5.7)]*.

Gastrointestinal Effects

Inform patients that TREXIMET, like other NSAID-containing products, may cause gastrointestinal discomfort and, rarely, serious gastrointestinal side effects such as ulcers and bleeding, which may result in hospitalization and even death. Although serious gastrointestinal tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding and should ask for medical advice if any indicative sign or symptoms, including epigastric pain, dyspepsia, melena, and hematemesis, are observed. Apprise patients of the importance of this follow-up *[see Warnings and Precautions (5.2)]*.

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 (5.12)]*.

Serious Skin Reactions

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, and toxic epidermal necrolysis, 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 the drug immediately if they develop any type of rash and contact their healthcare providers as soon as possible *[see Warnings and Precautions (5.13)]*.

Pregnancy

Inform patients that TREXIMET should not be used during the third trimester of pregnancy because NSAID-containing products have been shown to cause premature closure of the ductus arteriosus. Inform patients that TREXIMET should be used during the first and second trimester of pregnancy only if the potential benefit justifies the potential risk to the fetus *[see Contraindications (4), Warnings and Precautions (5.14), Use in Specific Populations (8.1)]*.

Nursing Mothers

Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed *[see Use in Specific Populations (8.3)]*.

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). Instruct patients to stop therapy and seek immediate medical therapy if these signs and symptoms occur *[see Warnings and Precautions (5.15)]*.

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, 7.3)]*.

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 (5.10), Drug Interactions (7.3, 7.6)]*.

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 (5.9)]*.

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.

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 (5.17)]*.

Fluid Retention/Weight Gain

Instruct patients to promptly report signs or symptoms of unexplained weight gain or edema to their healthcare providers.

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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]).**

**Your chance of a heart attack or stroke increases** with longer use of NSAID medicines or if you have heart disease.

**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 should never be used if you have ever had a heart surgery called a coronary artery bypass graft (CABG).**

**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:**

- the use of medicines called steroid hormones and blood thinners
- more frequent use
- drinking alcohol
- having poor health
- 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 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 have ever had 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.
- third trimester of pregnancy
- 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 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. **TREXIMET should not be used by pregnant women during the third trimester of their 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.

o 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)
- 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
- sudden or severe stomach pain
- blood in your bowel movement or it is black and sticky like t
- unusual weight gain
- flu-like symptoms

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: dextrose monohydrate, lecithin, maltodextrin, and sodium carboxymethylcellulose.
10/60-mg tablets also contain: polyethylene glycol and polyvinyl alcohol.

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