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
- 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.

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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,

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