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

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

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

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