CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203496Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ORENITRAM™ safely and effectively. See Full Prescribing Information for ORENITRAM.

ORENITRAM (treprostinil) Extended Release Tablets for oral administration
Initial U.S. Approval: 2002

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

Orenitram is a prostacyclin vasodilator indicated for:

- Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). (1.1)

As the sole vasodilator, the effect on exercise is small. Orenitram has not been shown to add to other vasodilator therapy. (1.1)

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

- Give with food. Swallow tablets whole; use only intact tablets. (2.1)
- Starting dose: 0.25 mg BID. (2.1)
- Titrate by 0.25 mg or 0.5 mg BID or 0.125 mg TID, not more than every 3 to 4 days as tolerated. (2.1)
- Maximum dose is determined by tolerability. (2.1)
- Mild hepatic impairment (Child Pugh Class A): Initiate at 0.125 mg BID. Increment at 0.125 mg BID every 3 to 4 days. (2.1)
- Avoid use in patients with moderate hepatic impairment. (2.1)

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

Extended Release Tablets: 0.125 mg, 0.25 mg, 1 mg and 2.5 mg. (3)

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

- Severe hepatic impairment (Child Pugh Class C). (4)

----------WARNINGS AND PRECAUTIONS----------

- Do not abruptly discontinue dosing. (2.2, 5.1)
- Increased risk of bleeding, particularly in patients receiving anticoagulants. (5.2)
- Do not take Orenitram with alcohol (5.3)
- In patients with diverticulosis Orenitram tablets can become lodged in a diverticulum. (5.4)

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

Most common adverse reactions (incidence >10%) reported in clinical studies with Orenitram are headache, nausea, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact United Therapeutics Corp. at 1-866-458-6479 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Blood pressure lowering drugs (e.g., diuretics, antihypertensive agents, or vasodilators): Risk of hypotension (7.1)
- When co-administered with strong CYP2C8 inhibitors the initial dose is 0.125 mg BID with 0.125 mg BID dose increments every 3 to 4 days. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescr bing information are not listed

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

Orenitram is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%).

When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this. Orenitram is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but this use has not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Orenitram is supplied as extended release tablets. Individualize dosing of Orenitram according to clinical response.

The recommended starting dose of Orenitram is 0.25 mg twice daily (BID) with food, taken approximately 12 hours apart. Increase the dose as tolerated to achieve optimal clinical response. The recommended increment is 0.25 or 0.5 mg BID every 3-4 days. If 0.25 mg BID dose increments are not tolerated consider titrating slower. The total daily dose can be divided and given three times daily with food (TID; approximately 8 hours apart), titrating by increments of 0.125 mg TID.

The maximum dose is determined by tolerability. The mean dose in a controlled clinical trial at 12 weeks was 3.4 mg BID. Maximum doses studied were 12 mg BID in the 12-week blinded study and up to 21 mg BID in an open-label long-term study.

If intolerable pharmacologic effects occur, decrease the dose in increments of 0.25 mg. Avoid abrupt discontinuation *[see Warnings and Precautions (5.1)]*.

Hepatic impairment: In patients with mild hepatic impairment (Child Pugh Class A) start at 0.125 mg BID with 0.125 mg BID dose increments every 3 to 4 days. Avoid use of Orenitram in patients with moderate hepatic impairment (Child Pugh Class B). Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C) *[see Contraindications (4), Warnings and Precautions (5.4), Use in Specific Populations (8.6),* and *Clinical Pharmacology (12.3)]*.

Concomitant administration with CYP2C8 inhibitors: When co-administered with strong CYP2C8 inhibitors (e.g., gemfibrozil) the initial dose is 0.125 mg BID with 0.125 mg BID dose increments every 3 to 4 days.

Take Orenitram with food. Swallow Orenitram intact; use only intact tablets.

2.2 Interruptions and Discontinuation

If a dose of medication is missed, take the missed dose as soon as possible, with food. If a patient misses two or more doses, restart at a lower dose and re-titrate.

In the event of a planned short-term treatment interruption for patients unable to take oral medications, consider a temporary infusion of subcutaneous or intravenous treprostinil. To calculate the total daily dose (mg) of treprostinil for the parenteral route divide the oral total daily dose by 5.

When discontinuing Orenitram, reduce the dose in steps of 0.5 to 1 mg per day *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Orenitram (treprostinil extended-release) is available in the following four strengths:

- 0.125 mg [White tablet imprinted with UT 0.125]
- 0.25 mg [Green tablet imprinted with UT 0.25]
- 1 mg [Yellow tablet imprinted with UT 1]
- 2.5 mg [Pink tablet imprinted with UT 2.5]

4 CONTRAINDICATIONS

Severe hepatic impairment (Child Pugh Class C) *[see Use In Specific Populations (8.6)* and *Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening PAH Symptoms upon Abrupt Withdrawal

Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms.

5.2 Risk of Bleeding

Orenitram inhibits platelet aggregation and increases the risk of bleeding.

5.3 Increased Exposure with Alcohol

Do not take Orenitram with alcohol as release of treprostinil from the tablet may occur at a faster rate than intended.

5.4 Use in Patients with Blind-end Pouches

The tablet shell does not dissolve. In patients with diverticulosis, Orenitram tablets can lodge in a diverticulum.

6 ADVERSE REACTIONS

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 to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In a 12-week placebo-controlled monotherapy study (Study 1; WHO Group 1; functional class II-III), the most commonly reported adverse reactions that occurred in patients receiving Orenitram included: headache, nausea, and diarrhea. Table 1 lists the adverse reactions that occurred at a rate on Orenitram at least 5% higher than on placebo.

Orenitram patients in Table 1 for Study 1 (N = 151) had access to 0.25 mg tablets at randomization. Approximately 91% of such patients experienced an adverse reaction, but only 4% discontinued therapy for an adverse reaction (compared to 3% receiving placebo). The overall discontinuation rate for any reason was 17% for active and 14% for placebo.

Table 1: Adverse Reactions with Rates at Least 5% Higher on Orenitram Monotherapy than on Placebo

Reaction	Orenitram N=151	Placebo N=77
Headache	63%	19%
Diarrhea	30%	16%
Nausea	30%	18%
Flushing	15%	6%
Pain in jaw	11%	4%
Pain in extremity	14%	8%
Hypokalemia	9%	3%
Abdominal discomfort	6%	0%

Orenitram was studied in a long-term, open-label extension study in which 824 patients were dosed for a mean duration of approximately 2 years. About 70% of patients continued treatment with Orenitram for at least a year. The mean dose was 4.2 mg BID at one year. The adverse reactions were similar to those observed in the placebo-controlled trials.

7 DRUG INTERACTIONS

7.1 Antihypertensive Agents or Other Vasodilators

Concomitant administration of Orenitram with diuretics, antihypertensive agents or other vasodilators increases the risk of symptomatic hypotension.

7.2 Anticoagulants

Treprostinil inhibits platelet aggregation; there is increased risk of bleeding, particularly among patients receiving anticoagulants.

7.3 Effect of CYP2C8 Inhibitors

Co-administration of Orenitram and the CYP2C8 enzyme inhibitor gemfibrozil in healthy adult volunteers increases exposure to treprostinil. Reduce the starting dose of Orenitram to 0.125 mg BID and use 0.125 mg BID increments every 3 to 4 days *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Animal reproductive studies with treprostinil diolamine have shown an adverse effect on the fetus. There are no adequate and well-controlled studies in humans.

DOCKET ALARM

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