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 use
Initial U.S. Approval: 2002

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

- Dosage and Administration (2.2) 01/2017

---------- **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 or 0.125 mg TID. (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)
- If transitioning from intravenous (IV) or subcutaneous (SC) Remodulin, the Orenitram dose should be increased while simultaneously decreasing the IV/SC infusion rate. (2.2)
- Mild hepatic impairment (Child Pugh Class A): Initiate at 0.125 mg BID. Increment at 0.125 mg BID every 3 to 4 days. (2.3)
- Avoid use in patients with moderate hepatic impairment. (2.3)

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

Extended-Release Tablets: 0.125 mg, 0.25 mg, 1 mg, 2.5 mg and 5 mg. (3)

---------- **CONTRAINDICATIONS** ----------

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

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

- Do not abruptly discontinue dosing. (2.5, 5.1)
- Increased risk of bleeding, particularly in patients receiving anticoagulants. (5.2)
- In patients with diverticulosis Orenitram tablets can become lodged in a diverticulum. (5.3)

---------- **ADVERSE REACTIONS** ----------

Most common adverse reactions (incidence >5%) reported in clinical studies with Orenitram are headache, diarrhea, nausea, and flushing. (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. (2.4, 7.3)

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

Revised: 01/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Take Orenitram with food. Swallow Orenitram tablets whole; do not crush, split, or chew.

The recommended starting dose of Orenitram is 0.25 mg twice daily (BID) with food, taken approximately 12 hours apart or 0.125 mg three times daily (TID) with food, taken approximately 8 hours apart. Increase the dose to the highest tolerated dose. The recommended increment is 0.25 or 0.5 mg BID or 0.125 mg TID every 3-4 days. If dose increments are not tolerated consider titrating slower.

The appropriate maintenance dose is determined by tolerability.

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

2.2 Transitioning from Subcutaneous or Intravenous Routes of Administration of Treprostinil

Decrease the dose of Remodulin while simultaneously increasing the dose of Orenitram. The dose of Remodulin can be reduced up to 30 ng/kg/min per day and the dose of Orenitram simultaneously increased up to 6 mg per day (2 mg TID) if tolerated. The following equation can be used to estimate a comparable total daily dose of Orenitram in mg using a patient's dose of IV/SC treprostinil (in ng/kg/min) and weight (in kg).

Orenitram total daily dose (mg) = 0.0072 X Remodulin dose (ng/kg/min) X weight (kg)

2.3 Dose Adjustment in Patients with 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), Use in Specific Populations (8.6),* and *Clinical Pharmacology (12.3)]*.

2.4 Dose Adjustment for Use 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.

2.5 Interruptions and Discontinuation

If a dose of medication is missed, the patient should 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 use the following equation:

$$\text{Remodulin (ng/kg/min)} = \frac{139 \text{ X Orenitram total daily dose (mg)}}{\text{weight (kg)}}$$

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 tablets are available in the following five 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]
- 5 mg [Red tablet imprinted with UT 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 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, diarrhea, nausea, and flushing. Table 1 lists the most common 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.

The safety of Orenitram was also evaluated in an open-label study transitioning patients from Remodulin. The safety profile during this study was similar to that observed in the three pivotal studies.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during postapproval use of Orenitram: dizziness, dyspepsia, vomiting, myalgia, and arthralgia. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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 (2.4) 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.

In rats, treatment with treprostinil diolamine had no effect on reproductive performance or sperm motility at doses up to 10 mg/kg/day. The exposures at this dose level are about 10- (male) to 18- (female) fold the usual human exposure at the mean dose of 3.4 mg BID.

In pregnant rats, reversible, dose-dependent decreases in body weight gain and food consumption were observed during the first four days of dosing in animals administered 10, 20 and 30 mg/kg/day treprostinil diolamine. In a dose range-finding study, there was a 17% decrease in the pregnancy rate in the animals administered 20 and 30 mg/kg/day. One dam in each of the 20 and 30 mg/kg/day had litters with no viable fetuses. In the definitive study (0, 5, 10 and 20 mg/kg/day), there were four treatment-related deaths, and a 32% decrease in the pregnancy rate for rats administered 20 mg/kg/day. There was an 8% decrease in the pregnancy rate in the animals administered 10 mg/kg/day. Across both studies, an increase in post-implantation loss was observed in animals administered 10 to 30 mg/kg/day, and a significant decrease in the mean number of live births was seen at dose levels ≥10 mg/kg/day. The no observed adverse effect level was 5 mg/kg/day (maternal, fetal viability and growth), and 20 mg/kg/day (teratogenicity), the highest dose tested in the definitive study. The exposures at 5 and 20 mg/kg/day doses represent 13 and 55 times, respectively, the human exposure.

For F_1 progeny, a decreased copulation index was observed at the 5 and 10 mg/kg/day treprostinil diolamine dose levels in rats. The no observed effect levels for physical development, reflex development, exploratory behavior, learning and memory, and sexual maturation was 10 mg/kg/day. The no observed effect level for F_1 progeny general development (based on body weight) was 10 mg/kg/day for females and ≤ 2.5 mg/kg/day for males; the no observed effect level for F_1 reproductive performance was 2.5 mg/kg/day or 6 times the human exposure.

In pregnant rabbits, the primary maternal adverse effects were gastrointestinal disturbance; dose-dependent decreases in mean body weight, body weight gain, and food consumption were observed. During the post-dose phase, the effect was reversed. In a dose range-finding study, there was a 17% decrease in the pregnancy rate for animals administered 4 mg/kg/day. A dose-dependent increase in post-implantation loss was observed. Two dams administered 4 mg/kg/day had litters with no viable fetuses; the mean fetal weight was slightly decreased in animals administered 4 mg/kg/day. In the definitive study, mean fetal weights were significantly decreased in animals administered 0.5 to 3 mg/kg/day of treprostinil diolamine. At doses of 1.5 and 3 mg/kg/day, external fetal and soft tissue malformations were observed in a few fetuses, and the total fetal skeletal malformations were significantly increased. The no observed adverse effect level was less than 0.5 mg/kg/day (maternal), 1.5 mg/kg/day (fetal viability and growth), and 0.5 mg/kg/day (teratogenicity). The 0.5 mg/kg/day dose represents about 5 times the human exposure.

8.2 Labor and Delivery

The effect of Orenitram on labor and delivery in humans is unknown. No treprostinil treatment-related effects on labor and delivery were seen in animal studies.

8.3 Nursing Mothers

It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, choose Orenitram or breastfeeding.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

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