- Give with food. Swallow tablets whole; use only intact tablets. (2.1)
- Starting dose: 0.125 mg TID or 0.25 mg BID. (2.1)
- Titrate by 0.125 mg TID or by 0.25 mg or 0.5 mg BID, not more frequently than every 3 to 4 days as tolerated. (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 not more frequently than every 3 to 4 days. (2.3)
- Avoid use in patients with moderate hepatic impairment. (2.3)

www.fda.gov/medwatch.

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

- When co-administered with strong CYP2C8 inhibitors the initial dose is 0.125 mg BID with 0.125 mg BID dose increments not more frequently than every 3 to 4 days. (2.4, 7.1)

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

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Pulmonary Arterial Hypertension
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing
2.2 Transitioning from Subcutaneous or Intravenous Routes of Administration of Treprostinil
2.3 Dose Adjustment in Patients with Hepatic Impairment
2.4 Dose Adjustment for Use with CYP2C8 Inhibitors
2.5 Interruptions and Discontinuation
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Worsening PAH Symptoms upon Abrupt Withdrawal
5.2 Use in Patients with Blind-end Pouches
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Post-Marketing Experience
7 DRUG INTERACTIONS
7.1 Effect of CYP2C8 Inhibitors on Treprostinil
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Hepatic Impairment
8.7 Patients with Renal Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Clinical Trials in Pulmonary Arterial Hypertension
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage
17 PATIENT COUNSELING INFORMATION

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

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 0.125 mg three times daily (TID) with food, taken approximately 8 hours apart or 0.25 mg twice daily (BID) with food, taken approximately 12 hours apart.

Titrate by 0.125 mg TID or 0.25 or 0.5 mg BID not more frequently than every 3 to 4 days. Increase the dose to the highest tolerated dose.

If dose increments are not tolerated, consider titrating slower. If intolerable pharmacologic effects occur, decrease the dose in increments of 0.125 mg TID or 0.25 mg BID. 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 target total daily dose of Orenitram in mg using a patient's dose of intravenous (IV)/subcutaneous (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 not more frequently than 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) due to increases in systemic exposure *[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 not more frequently than every 3 to 4 days.

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 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), and an event-driven, placebo-controlled, combination therapy study (Study 4; WHO Group 1; functional class I-III), the most commonly reported adverse reactions that occurred in patients receiving Orenitram included: headache, diarrhea, nausea, and flushing.

on Placebo in Either Study 1 or Study 4

Reaction	Study 1 N=228[a]		Study 4 N=690	
	Orenitram n=151	Placebo n=77	Orenitram n=346	Placebo n=344
Headache	63%	19%	75%	35%
Diarrhea	30%	16%	69%	29%
Nausea	30%	18%	40%	23%
Vomiting	17%	16%	36%	10%
Flushing	15%	6%	45%	8%
Pain in jaw	11%	4%	18%	3%
Pain in extremity	14%	8%	18%	9%
Hypokalemia	9%	3%	4%	3%
Abdominal discomfort	6%	0%	8%	4%
Upper abdominal pain	5%	3%	12%	5%

[a] Includes all subjects in the Primary Analysis Population

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

8.1 Pregnancy

Risk Summary

Limited published data from case reports with Orenitram use in pregnant women are not sufficient to assess for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with pulmonary arterial hypertension *(see Clinical Considerations)*. Animal reproductive studies with treprostinil diolamine administered orally have shown an adverse effect on the fetus. In rats, administration of treprostinil to pregnant rats during the period of organogenesis at doses ≥10 mg/kg/day (approximately 15 times the human exposure at the dose of 3.5 mg BID on an AUC basis) resulted in decreased pregnancy rate, increased post-implantation loss, and decreased fetal viability and growth. In rabbits, teratogenicity and decreased fetal viability and growth were observed at doses ≥1.5 mg/kg/day (approximately 7 times the human exposure at the dose of 3.5 mg BID on an AUC basis) *(see Animal Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Pulmonary arterial hypertension in pregnancy increases the risk of maternal heart failure, stroke and death, preterm delivery, low birth weight, and stillbirth.

Data

Animal Data

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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.