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treprostinil
EXTENDED-RELEASE TABLETS

90-DAY TRIAL PROGRAM

FOR YOUR FC II-III PATIENTS WITH PAH (WHO GROUP 1)

The Orenitram® 90-Day Trial Program

allows eligible patients* to try Orenitram at no cost for up to 90 days

See the **PATIENT LEAFLET** inside the pocket (page 7)

Patients are under no obligation to continue taking Orenitram after the trial period.

BUSINESS CARD HOLDER GLUES HERE

INDICATION

Orenitram is a prostacyclin mimetic indicated for treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to delay disease progression and to improve exercise capacity. The studies that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (66%) or PAH associated with connective tissue disease (26%).

IMPORTANT SAFETY INFORMATION

Contraindications

- Avoid use of Orenitram in patients with severe hepatic impairment (Child Pugh Class C) due to increases in systemic exposure.

Please see additional Important Safety Information throughout and the Full Prescribing Information and Patient Information for Orenitram in pocket.

*See eligibility criteria on pages 2 and 3.

FC=functional class; PAH=pulmonary arterial hypertension; WHO=World Health Organization.

THE ORENITRAM 90-DAY TRIAL PROGRAM

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The Orenitram 90-Day Trial Program allows you to assess how your patients will do on Orenitram. The program is offered at no cost for up to 90 days, and your patients have no obligation to continue taking Orenitram at the end of the trial period.

To enroll your eligible patients, simply follow the 4 steps below or reach out to your United Therapeutics rep for more information

Get started with just 4 steps

1. Complete the Orenitram 90-Day Trial Program enrollment form in its entirety, including:
   a. Patient and physician information
   b. Physician Attestation form stating that the patient has PAH (WHO Group 1) and is eligible for the program
   c. Required dosing regimen and adverse events management recommendations
2. Complete patient release form, including patient signature
3. Fax completed forms to ASSIST® at 1-800-380-5294
4. Answer phone calls to provide missing and/or necessary information to ASSIST and the Orenitram 90-Day Trial Program pharmacy

Eligibility for this program is limited to patients with PAH (WHO Group 1) who have never been treated with Orenitram. Patients transitioning from another treprostinil medication are not eligible for this program. For other eligibility criteria, see full Terms & Conditions for the program on the next page.

To get your patient started, submit the enclosed enrollment and patient release forms

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

SUPPORT EVERY STEP OF THE WAY

Once you submit an Orenitram 90-Day Trial Program enrollment form, ASSIST will reach out to eligible patients to:

- Obtain any additional information needed
- Provide information about what to expect from the 90-Day Trial Program
- Connect your patient with the Orenitram 90-Day Trial Program pharmacy that will arrange for medication delivery

Upon approval, the Orenitram 90-Day Trial Program pharmacy will help your patients get started on Orenitram by scheduling:

- 3 nurse visits to provide ongoing support on how to take Orenitram
- Home delivery of their medication throughout the program

assist Access Solutions and Support Team

TO CONTACT ASSIST, CALL 1-877-UNITHER (1-877-864-8437)

Tracking patient progress

Around day 60 of the **90-Day Trial Program**, ASSIST will get in touch with you to see if you would like your patient to continue in the program and keep Orenitram as part of the patient's treatment plan. **If you decide not to continue your patient in the program, that patient will have to be down-titrated to avoid abrupt discontinuation of Orenitram.** For more information on down-titrating Orenitram, see the dosing section on page 4 of this brochure.

Taking steps beyond 90 days

Your patient is under no obligation to continue taking Orenitram after the trial period. If you decide to continue your patient on Orenitram beyond the 90-day trial, an Orenitram referral form must be submitted to ASSIST. ASSIST will then complete all required steps to process your referral and help your patient continue taking Orenitram. **Please keep in mind that your patient's insurance may require him or her to have tried either a PDE-5i or ERA prior to starting Orenitram.**

NOTE: While specific testing (eg, right heart catheterization, hemodynamic testing) is not required for submission of the 90-Day Trial Program enrollment form, testing will be required to process an Orenitram referral form submission (visit Orenitram.com/HCP for more information on the referral process).

ORENITRAM 90-DAY TRIAL PROGRAM TERMS & CONDITIONS

The Orenitram 90-Day Trial Program ("Trial Program") is offered by United Therapeutics Corporation. To utilize this Trial Program, you must have a valid prescription for an FDA-approved use of Orenitram. There is no obligation to continue Orenitram after the 90-Day Trial Program. If the decision is made to continue therapy, a separate prescription must be written by your healthcare provider and dispensed by one of United Therapeutics Corporation's contracted specialty pharmacies, Accredo or CVS Specialty. Patients may be offered the Trial Program exclusively through their healthcare provider.

TERMS AND CONDITIONS FOR TRIAL PROGRAM

By enrolling in the 90-Day Trial Program for Orenitram, you acknowledge that you currently meet the eligibility criteria and will comply with the Terms and Conditions described below:

1. Only new patients with a valid prescription for an FDA-approved use of Orenitram may use this Trial Program. This **Trial Program** is not valid for patients transitioning to Orenitram from Tyvaso or Remodulin. By enrolling in this Trial Program, you certify that: (a) you are not currently using and have not previously used Orenitram outside of the hospital setting (i.e. "Outpatient"), and (b) you are not currently taking an inhaled or infused prostacyclin.
2. Patients are not eligible to start the Trial program in the hospital setting (i.e. "Inpatient").
3. Product cannot be shipped to a hospital, physician's office, etc. Product must be shipped directly to the patient.
4. This offer is only valid for those patients 18 years and older.
5. Only 1 enrollment per patient may be redeemed under this program; no photocopies or reproductions of the enrollment form will be accepted.
6. Enrollment is valid for 90 days of Orenitram at no cost to the patient.
7. **No claim for reimbursement for product dispensed pursuant to this Trial Program may be submitted, in whole or part, to any third-party payer, including a public or private payer.**
8. The prescription for the Trial Program cannot be submitted to count towards out of pocket costs under any prescription medicine plan.
9. For Medicare patients, Trial Program product may not count towards "True Out-of-Pocket (TrOOP)" expenses.
10. The Trial Program enrollment form will be accepted only at United Therapeutics Corporation's contracted pharmacy for this Program, Lash and Group. Offer not valid if submitted to any other pharmacy.
11. This enrollment form is not transferable. It is illegal for any person to sell, purchase, or trade, or offer to sell, purchase, or trade or to counterfeit this voucher.
12. This 90-Day Trial Program cannot be combined with any other rebate/coupon, free trial, or similar offer for the specified prescription.
13. **This free trial is not health insurance.**
14. United Therapeutics Corporation makes no express or implied guarantee that Orenitram will be covered by any third-party payer after the 90-day trial period.
15. Offer good only in the United States and Puerto Rico.
16. United Therapeutics Corporation reserves the right to rescind, revoke, or amend this free trial program at any time without notice.

Please see additional Important Safety Information throughout and the Full Prescribing Information and Patient Information for Orenitram in pocket.

ERA=endothelin receptor antagonist; PDE-5i=phosphodiesterase type 5 inhibitor.

DOSE INITIATION WITH ORENITRAM

Initiate early (FC II or FC III) when patients have adequate time to titrate[1]

Initiate
at the starting dose of 0.125 mg TID taken every 8 hours[1]

Titrate
gradually with ~weekly increases of 0.125 mg TID*†

Elevate
dose to achieve appropriate therapeutic benefits

If not tolerated, try slowing or temporarily stopping titration. You can also down-titrate if needed. Avoid abrupt discontinuation.[1]

If you decide to discontinue Orenitram during the Trial Program, reduce the dose in increments of 0.5 mg to 1 mg per day.[1]

Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms.[1]

5 tablet strengths offer flexibility to titrate to clinical response and tolerability, with no labeled maximum dose[1]

Tablets not shown at actual size.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

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

Adverse Reactions

- In the 12-week, placebo-controlled, monotherapy study, and an event-driven, placebo-controlled, combination therapy study, adverse reactions that occurred at rates at least 5% higher on Orenitram than on placebo included headache, diarrhea, nausea, vomiting, flushing, pain in jaw, pain in extremity, hypokalemia, abdominal discomfort, and upper abdominal pain.

Drug Interactions

- Co-administration of Orenitram and the CYP2C8 enzyme inhibitor gemfibrozil increases exposure to treprostinil; therefore, Orenitram dosage reduction may be necessary in these patients.

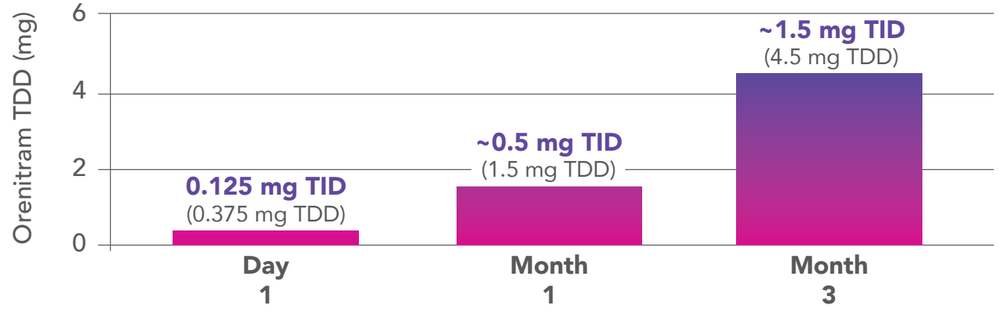
*Titrate no more frequently than every 3 to 4 days.[1]
†You can also choose a BID (~12 hours apart) dosing schedule, starting at 0.25 mg BID and titrating in 0.25 mg BID increments as tolerated.[1]

BID=2 times daily; TID=3 times daily.

DOSE TITRATION WITH ORENITRAM

Consider TID dosing to help reduce peak-to-trough fluctuations and improve tolerability[1]

Example Titration Schedule for 90 Days[1]



Dosing considerations

Similar to parenteral therapy, titrate Orenitram to clinical response based on how your patients tolerate the medication.[1]

When adverse events occur, consider time between doses, speed of titration, and proactive adverse events management.[1,2]

It's important that your patients swallow their Orenitram tablets whole, take them with food, and do not skip any doses.[1]

Learn more about Orenitram dosing at Orenitram.com/HCP

IMPORTANT SAFETY INFORMATION

Specific Populations

- Animal reproductive studies with Orenitram have shown an adverse effect on the fetus. There are no adequate and well-controlled studies with Orenitram in pregnant women.
- It is not known whether treprostinil is excreted in human milk or if it affects the breastfed infant or milk production.

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TDD=total daily dose.

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COMMON ADVERSE EVENTS

Adverse Events With Rates at Least 5% Higher on Orenitram Therapy Than on Placebo in FREEDOM-EV (N=690)[1]

Reaction	Orenitram (n=346)	Placebo (n=344)
Headache	75%	35%
Diarrhea	69%	29%
Flushing	45%	8%
Nausea	40%	23%
Vomiting	36%	10%
Pain in jaw	18%	3%
Pain in extremity	18%	9%
Upper abdominal pain	12%	5%

19% of patients on Orenitram and 4% of those receiving placebo discontinued treatment due to adverse events [1]

TIPS

List your preferred adverse events management strategies on the enrollment form

Your recommended adverse events management strategies will be communicated to the pharmacy.

Proactively manage adverse events with your patient

Use the enclosed patient leaflet to review and record your recommended adverse events management strategies with your patient. Remind your patient to consult this brochure and call your office if he or she experiences adverse events.

IMPORTANT SAFETY INFORMATION

Specific Populations (cont)

- Safety and effectiveness of Orenitram in pediatric patients have not been established.
- Use of Orenitram in patients aged 65 years and over demonstrated slightly higher absolute and relative adverse event rates compared to younger patients. Caution should be used when selecting a dose for geriatric patients.
- There is a marked increase in the systemic exposure to treprostinil in hepatically impaired patients.

ADVERSE EVENTS MANAGEMENT STRATEGIES

Setting patient expectations for adverse events with Orenitram and developing a management plan to mitigate their effects may help patients stay with therapy[2,3]

Strategies to help patients manage adverse events and achieve a higher maximum dose[1,2]

- Take Orenitram with food
- Reduce dosage
- Slowing titration
- Proactive use of adjunctive pharmacotherapy

Proactive use of adjunctive interventions should be considered in managing adverse events from the start[2]

Delphi Consensus Recommendations for Select Adverse Events Management[2]*

Headache	Nausea	Diarrhea
• Acetaminophen • Tramadol† • Opioids†‡ • Gabapentin† • NSAIDs†	• Take with food • Ondansetron† • PPIs† • Promethazine† • Prochlorperazine† • Metoclopramide†	• Diphenoxylate/Atropine† • Loperamide • Add fiber to diet • Dicyclomine†

Recommendations to aid in side effect management were assembled using the Delphi process, a structured communication technique that gathered information from a panel of respondents with expertise using Orenitram (N=11). In this independent analysis, the Delphi process was used to investigate best practices used by panelists for side effect management in patients treated with Orenitram. Survey participants were from 11 centers and had a total experience of 206 patients.[2]

United Therapeutics does not provide medical advice

Side effect management strategies should be dealt with in accordance with the Orenitram Full Prescribing Information and your clinical judgment.

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*Consensus recommendations state that reassurance will suffice for flushing or jaw pain.[2]
†Separate prescription required.
‡Only recommended in severe cases.

NSAID=nonsteroidal anti-inflammatory drug; PPI=proton pump inhibitor.

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References: 1. Orenitram [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2019. **2.** Rahaghi FF, Feldman JP, Allen RP, et al. Recommendations for the use of oral treprostinil in clinical practice: a Delphi consensus project pulmonary circulation. *Pulm Circ.* 2017;7(1):167-174. **3.** Data on file. United Therapeutics Corporation. Research Triangle Park, NC.

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