Partnering with your patients taking Orenitram

A guide to best practices for helping to manage adverse events associated with Orenitram

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 on page 8 and the Full Prescribing Information and Patient Information for Orenitram in pocket.

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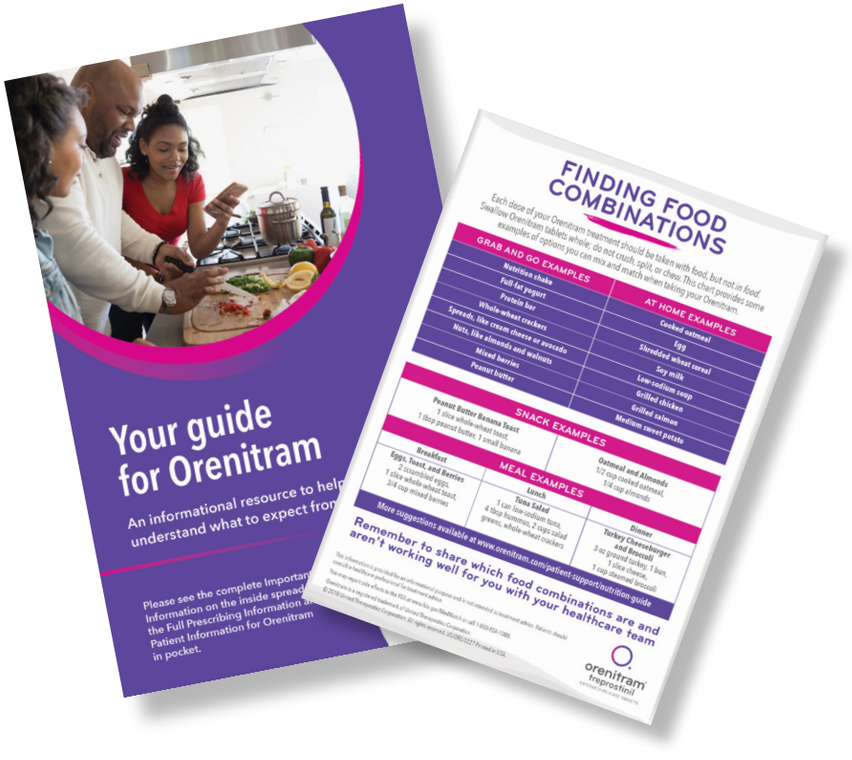
The importance of working closely with your patients

Orenitram, a prostacyclin-class therapy, has been shown to delay disease progression and improve several measures of symptoms and function in patients with pulmonary arterial hypertension (PAH). However, because of the wide-ranging effects of prostacyclin in the body, Orenitram is likely to cause certain adverse events.[1-3]

In this brochure, you will learn about the importance of partnering with your patients to help ensure that adverse events are successfully managed so they can experience the benefits of treatment with Orenitram. We've also enclosed pamphlets that you can give to patients as a way to reinforce the information you are sharing with them.



IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

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Common adverse events with Orenitram

In FREEDOM-EV, adverse events were consistent with previous studies of Orenitram and known prostacyclin-related adverse events[1,4-7]*

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%

FREEDOM-EV was an international, multicenter, randomized, double-blind, placebo-controlled, event-driven clinical worsening study in patients with PAH receiving background oral monotherapy (PDE-5i, sGCS, or ERA).[1]

For some medications, patients may experience adverse events before the benefits of treatment are realized. Setting expectations on therapy can help patients feel more prepared.

- Make patients aware of typical adverse events so they know what to expect and may be more likely to stay with treatment
- Explain that adverse events may be worse when starting Orenitram or after a dose increase[2]
- Reassure patients that adverse events may be managed with adjunctive pharmacologic or nonpharmacologic methods[8]

Even though patients experienced adverse events in FREEDOM-EV, most patients stayed in the study. Nineteen percent of patients on Orenitram and 4% of those receiving placebo discontinued treatment due to adverse events. Discontinuation due to an adverse event was more common in the first 24 weeks of treatment.[1,2]

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.

*Previous studies included FREEDOM-M, FREEDOM-C, FREEDOM-C2, and FREEDOM-EXT.[1,4-7]

ERA=endothelin receptor antagonist; PDE-5i=phosphodiesterase type 5 inhibitor; sGCS=soluble guanylate cyclase stimulator.

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How you dose Orenitram can affect tolerability

There are strategies you can incorporate as part of the titration process to help your patients reach an appropriate dose while minimizing side effects[8]

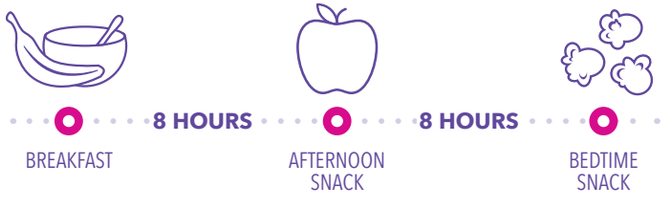
Use a TID dosing schedule

- Orenitram is best tolerated when taken every 8 hours[1]
- A TID regimen (every 8 hours) may reduce peak-to-trough fluctuations as compared to a BID regimen[1]

Remind patients to take Orenitram with food

- Taking Orenitram with food can help maximize bioavailability[1]
- The magnet in the patient pamphlet is a handy reminder of this and offers suggestions for patients who may be looking for food ideas at home or on the go

Provide patients with guidance on how to make taking Orenitram TID with food part of their daily schedule[1]



- Patients can try varying the timing of their food or snack when taking Orenitram to see what is best tolerated
  - For example, patients can try eating 15 minutes before taking Orenitram or try taking Orenitram at the same time as their food

IMPORTANT SAFETY INFORMATION

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.

Please see additional Important Safety Information on page 8 and the Full Prescribing Information and Patient Information for Orenitram in pocket.

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

Titrate slowly or reduce the dose

- Increase dose by 0.125 mg TID ~weekly[1]*
  - Titrate more slowly if dose increases are not tolerated[1]

- Decreasing the dose may be necessary if intolerable adverse events occur[1]

Reinforce taking Orenitram as prescribed

It is important to emphasize taking the treatment exactly as prescribed:

- Swallow tablets whole[1]
  - Advise patients not to crush, split, or chew the tablets

- Avoid abrupt discontinuation of treatment, as this may result in worsening of PAH symptoms[1]

Advise patients to also work with their specialty pharmacy for additional support with taking Orenitram

IMPORTANT SAFETY INFORMATION

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.

*Not more frequently than every 3 to 4 days. If dosing BID, titrate 0.25 mg BID ~weekly.[1]

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Proactively manage adverse events

To help your patients manage adverse events and have a successful experience with treatment, it's necessary to develop a proactive management plan. This plan should be in place as soon as patients start Orenitram treatment.

Delphi consensus recommendations

The recommendations below are based on the real-world experience of experts in the field. It may be helpful to consider some of these when developing an adverse event management plan for your patient.[8]

Delphi Consensus Recommendations for Select Adverse Events Management[8]*

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

The guidelines were developed by a panel using the Delphi process. This is a structured communication technique that gathered information from a panel of respondents with expertise using Orenitram (N=11). Survey participants were from 11 centers and had a total experience of 206 patients.[8]

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.

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.

Please see additional Important Safety Information on page 8 and the Full Prescribing Information and Patient Information for Orenitram in pocket.

*Consensus recommendations state that reassurance will suffice for flushing or jaw pain.[8]
†Separate prescription required.
‡Only recommended in severe cases.

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

Have an open conversation with your patients

Establishing an open dialogue with your patients about managing adverse events associated with Orenitram is critical to help them be successful. In addition, regular follow-up with patients to see how they are managing therapy can help reinforce and build relationships.

A dialogue with your patients may include asking probing questions, such as:

1. What tools or techniques will you be using to help you remember to take Orenitram every 8 hours?
2. What support do you have at home to ensure you are successful with Orenitram?
3. What obstacles do you feel might get in the way of taking your medication on time? How can I help address them?
4. Do you understand what side effects you might expect with treatment?
5. Are you clear on what medications you should take to help manage side effects?
6. Do you understand why it is important to take your Orenitram exactly as prescribed and what benefits it will offer?
7. Are you clear how and when you should contact the office in case you do experience a side effect?

Have your patients use the back cover of the enclosed patient pamphlet to write down your recommendations for managing adverse events

By setting clear expectations about side effects with Orenitram, you can help ensure patients feel confident and comfortable with their treatment regimen.

IMPORTANT SAFETY INFORMATION

Specific Populations (cont)

- 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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Orenitram® (treprostinil) Extended-Release Tablets

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Drug Interactions

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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.
- 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.

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Please see Full Prescribing Information and Patient Information at www.orenitram.com or call 1-877-UNITHER (1-877-864-8437).

Help your patients know what to expect with these resources

Partner with your patients taking Orenitram

Have an open and honest discussion

regarding the side effects so your patients know what to expect

Proactively manage common adverse events

to help your patients stay with treatment

Educate patients on what to do

in case they experience adverse events

Follow up regularly with your patients

so you are aware of any adverse events and can offer management strategies if needed

IMPORTANT SAFETY INFORMATION

Specific Populations (cont)

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References: 1. Orenitram [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2019. **2.** Data on file. United Therapeutics Corporation. Research Triangle Park, NC. **3.** Kingman M, Archer-Chicko C, Bartlett M, et al. Management of prostacyclin side effects in adult patients with pulmonary arterial hypertension. *Pulm Circ.* 2017;7(3):598-608. **4.** Jing ZC, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized, controlled trial. *Circulation.* 2013;127(5):624-633. **5.** Tapson VF, Torres F, Kermeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial. *Chest.* 2012;142(6):1383-1390. **6.** Tapson VF, Jing ZC, Xu KF, et al; FREEDOM-C2 Study Team. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial. *Chest.* 2013;144(3):952-958. **7.** White RJ, Parikh K, Allen R, et al. EXPRESS: Long term study of oral treprostinil to treat pulmonary arterial hypertension: dosing, tolerability, and pharmacokinetics [published online July 10, 2019]. *Pulm Circ.* doi: 10.1177/2045894019866335. **8.** 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.

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