**Description:** Treprostinil is a unique prostacyclin molecule which causes direct vasodilation of pulmonary and systemic vasculature. It also inhibits platelet aggregation, including those in transition from Flolan (epoprostenol).

**Authorization Criteria:** pulmonary arterial hypertension

**Injection:** Treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in patients with NYHA class II-IV symptoms to decrease exercise-associated symptoms; to diminish clinical deterioration when transitioning from epoprostenol (I.V.)

**Inhalation:** Treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in patients with NYHA class III symptoms to improve exercise ability. **Note:** Nearly all controlled clinical trial experience has been with concomitant bosentan or sildenafil.

**Oral:** Treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in patients with WHO functional class II-III symptoms to improve exercise ability.

**Dosing:**

**Inhalation:** **Note:** Prior to initiation, patients should be carefully evaluated for ability to administer treprostinil and care for the inhalation system and accessories required for administration. Immediate access to a back-up inhalation device, accessories, and medication is essential to prevent treatment interruptions.

**Initial:** 18 mcg (or 3 inhalations) every 4 hours 4 times/day; if 3 inhalations are not tolerated, reduce to 1-2 inhalations, then increase to 3 inhalations as tolerated

**Maintenance:** If tolerated, increase dose by an additional 3 inhalations at approximately 1- to 2-week intervals; target dose and maximum dose: 54 mcg (or 9 inhalations) 4 times/day
Oral: Initial: 0.25 mg every 12 hours; may increase dose as tolerated in increments of 0.25 mg or 0.5 mg every 12 hours every 3-4 days to optimal clinical response. If 0.25 mg every 12 hour dose increments are not tolerated, consider slower titration. The total daily dose can also be given 3 times daily (~8 hours apart) and titrated in increments of 0.125 mg 3 times daily. Maximum dose is determined by tolerability. If intolerable effects occur, decrease dose in increments of 0.25 mg; avoid abrupt discontinuation. Upon discontinuation, reduce the dose in increments of 0.5 mg to 1 mg daily.

Missed doses: If a dose is missed, take the missed dose as soon as possible. If ≥2 doses are missed, restart at a lower dose and retitrade.

Dosage adjustment for concurrent use in patients receiving strong CYP2C8 inhibitors (gemfibrozil): Initiate a starting dose of 0.125 mg every 12 hours; increase in increments of 0.125 mg every 12 hours every 3-4 days.

Planned short-term treatment interruption: If patients are unable to continue oral treatment, a temporary infusion of subcutaneous or IV treprostinil may be considered. Divide the oral total daily dose by 5 to calculate the total daily dose (mg) of parenteral treprostinil.

SubQ (preferred) or IV infusion: Note: Prior to initiation, patients should be carefully evaluated for ability to administer treprostinil and care for the infusion system outside of inpatient setting. Immediate access to a back-up pump, infusion sets, and medication is essential to prevent treatment interruptions.

New to prostacyclin therapy: Initial: 1.25 ng/kg/minute; if dose cannot be tolerated due to systemic effects, reduce to 0.625 ng/kg/minute. Increase dose in increments of 1.25 ng/kg/minute per week for first 4 weeks, followed by increments of 2.5 ng/kg/minute per week for remainder of therapy. Limited experience with doses >40 ng/kg/minute. Note: Dose must be carefully and individually titrated (symptom improvement with minimal adverse effects). Avoid abrupt withdrawal. If infusion is restarted within a few hours of discontinuation, the same dose rate may be used. Interruptions for longer periods may require retitrination.

Transitioning from epoprostenol (see table): Note: Transition should occur in a hospital setting to follow response (eg, walking distance, sign/symptoms of disease progression).
May take 24-48 hours to transition. Transition is accomplished by initiating the infusion of treprostinil, and increasing it while simultaneously reducing the dose of intravenous epoprostenol. During transition, increases in PAH symptoms should be first treated with an increase in treprostinil dose. Occurrence of prostacyclin associated side effects should be treated by decreasing the dose of epoprostenol.

### Transitioning From IV Epoprostenol to SubQ (Preferred) or IV Treprostinil

<table>
<thead>
<tr>
<th>Step</th>
<th>Epoprostenol Dose</th>
<th>Treprostinil Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Maintain current dose</td>
<td>Initiate at 10% initial epoprostenol dose</td>
</tr>
<tr>
<td>2</td>
<td>Decrease to 80% initial dose</td>
<td>Increase to 30% initial epoprostenol dose</td>
</tr>
<tr>
<td>3</td>
<td>Decrease to 60% initial dose</td>
<td>Increase to 50% initial epoprostenol dose</td>
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<tr>
<td>4</td>
<td>Decrease to 40% initial dose</td>
<td>Increase to 70% initial epoprostenol dose</td>
</tr>
<tr>
<td>5</td>
<td>Decrease to 20% initial dose</td>
<td>Increase to 90% initial epoprostenol dose</td>
</tr>
<tr>
<td>6</td>
<td>Decrease to 5% initial dose</td>
<td>Increase to 110% initial epoprostenol dose</td>
</tr>
<tr>
<td>7</td>
<td>Discontinue epoprostenol</td>
<td>Maintain current dose plus additional 5% to 10% as needed</td>
</tr>
</tbody>
</table>

**Dosage Forms: U.S.**

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, Inhalation:
Tyvaso: 0.6 mg/mL (2.9 mL)
Tyvaso Refill: 0.6 mg/mL (2.9 mL)
Tyvaso Starter: 0.6 mg/mL (2.9 mL)

Solution, Injection:
Remodulin: 1 mg/mL (20 mL) [contains metacresol]
Remodulin: 2.5 mg/mL (20 mL); 5 mg/mL (20 mL); 10 mg/mL (20 mL) [contains metacresol, sodium chloride, sodium citrate]

Tablet Extended Release, Oral:
Orenitram: 0.125 mg, 0.25 mg, 1 mg, 2.5 mg [contains fd&c blue #2 (indigotine)]

**Contraindications/Warnings:** Chronic intravenous infusions are associated with the risk of blood stream infections, thrombus formation and sepsis, which may be fatal. Therefore, continuous subcutaneous infusion (undiluted) is the preferred mode of administration. Initiation of therapy must be performed in a setting with adequate personnel and equipment for physiological monitoring and emergency care. Abrupt withdrawal or sudden large reductions in dosage may result in worsening of PAH symptoms. Titrate slowly in patients with hepatic or renal insufficiency.

**Major Adverse Reactions:** Headache, nausea, emesis, restlessness, anxiety and infusion site pain/reaction

**Major Drug Interactions:** Anticoagulants potentiating bleeding risk; antihypertensives and vasodilators may potentiate vasodilation; gemfibrozil (Lopid) and rifampin increase levels of Remodulin.

**REFERENCES**


**Revision History:**

Date Approved by P&T Committee: 10/28/14; QAC 11/25/14
Date Reviewed/No Updates: 1/13/15 by C. Sanders, MD
Date Approved by P&T Committee: 1/27/15
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Date Approved by P&T Committee: 1/26/16
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Date Approved by P&T Committee: 1/24/17
Date Reviewed/No Updates: 1/23/18 by C. Sanders, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/23/18

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<td>Annual review</td>
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