Complex Therapy Management

- **General**
  - Accurate diagnosis
  - Initiation of therapy
  - Medication availability
  - Education and training
    - Staff
    - Patients
  - Cost and reimbursement
  - Limited distribution
  - Small populations
  - Contraindications

- **Prostacyclins (infused and inhaled):**
  - Unique devices and supplies
  - Complex dosing and titrations
  - Profound pharmacological effects
  - Specially-trained HCPs

- **Oral targeted therapies**
  - REMS
  - Drug interactions

Multidisciplinary Management

**UI Health PAH Team**
- Program Director
- PAH Nurse Coordinator
- Clinical Pharmacists
- Clinic Support Staff

**Health-System Approach**
- Physicians: pulmonary, critical care, cardiology
- Nurses: clinical and research
- Pharmacists: dispensing, clinical and research
- Research personnel
- Specialty services: rheumatology, hematology, hepatology, sleep medicine and cardiovascular imaging
What is the Hemodynamic Definition of Pulmonary Arterial Hypertension?

1. Mean PAP ≥25 mm Hg at rest or ≥30 mm Hg with exercise
2. Pulmonary artery systolic pressure >40 mm Hg
3. Mean PAP ≥25 mm Hg at rest, PCWP ≤15 mm Hg PVR, increased PVR
4. All of the above

PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance

Hemodynamic Definition of PH/PAH

PH
Mean PAP ≥25 mm Hg

PAH
Mean PAP ≥25 mm Hg plus
PCWP/LVEDP ≤15 mm Hg

ACCF/AHA includes PVR >3 Wood Units

LVEDP, left ventricular end diastolic pressure


5th World Symposium on PH: Modified Classification of PH

1. Pulmonary arterial hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
      1.2.1 BMPR2
      1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
      1.2.3 Unknown
   1.3 Drug- and toxin-induced
   1.4 Associated with
      1.4.1 Connective tissue disease
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart diseases (update)
      1.4.5 Schistosomiasis
      1.4.6 Chronic hemolytic anemia

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1'. PH/PPHN

2. PH due to LHD
   2.1 LV systolic dysfunction
   2.2 LV diastolic dysfunction
   2.3 Valvular disease
   2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to lung diseases and/or hypoxia
   3.1 COPD
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental lung diseases (update)

4. CTEPH

5. PH with unclear multifactorial mechanisms
   5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

### Hemodynamic-Clinical Classification Relationships

<table>
<thead>
<tr>
<th>Definition</th>
<th>Hemodynamic Characteristics</th>
<th>WHO Clinical Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>mPAP &gt;25 mm Hg&lt;br&gt;CO normal, reduced, or ↑</td>
<td>ALL</td>
</tr>
<tr>
<td>Pre-capillary PH</td>
<td>PCWP/LVEDP ≤15 mm Hg&lt;br&gt;TPG ≥12–15 mm Hg</td>
<td>1. PAH&lt;br&gt;3. PH due to lung disease and/or hypoxemia&lt;br&gt;4. CTEPH&lt;br&gt;5. PH with unclear or multifactorial mechanisms</td>
</tr>
<tr>
<td>Post-capillary PH</td>
<td>PCWP/LVEDP &gt;15 mm Hg&lt;br&gt;TPG &lt;12 mm Hg</td>
<td>2. PH owing to LHD</td>
</tr>
<tr>
<td>Mixed PH Reactive</td>
<td>PCWP/LVEDP &gt;15 mm Hg&lt;br&gt;TPG ≥12–15 mm Hg</td>
<td>2. PH owing to LHD</td>
</tr>
<tr>
<td>Mixed PH Non-reactive/fixed</td>
<td>PCWP/LVEDP &gt;15 mm Hg&lt;br&gt;TPG &lt;12 mm Hg</td>
<td>2. PH owing to LHD</td>
</tr>
</tbody>
</table>


### PAH Distributions in the US: REVEAL Registry

**Overall**
- Heritable (2.7%)
- Pulmonary veno-occlusive (0.4%)
- Idiopathic (40.2%)
- Associated (50.7%)

**Associated**
- HIV (4.0%)
- Other (5.5%)
- Connective tissue/collagen vascular (49.9%)
- Congenital heart disease (19.9%)
- Drug/Toxins (10.5%)
- Portopulmonary (10.6%)

Based on Venice Clinical Classification (2003); 2967 patients.

### Progressive and Life-limiting Disorder

Pathological changes in the pulmonary arteries

**Hemodynamic impairment**
- CO<br>mPAP<br>PVR

Decreasing mean PAP may not reflect improvement

Adapted from Gaine S. JAMA. 2003;289:3166-3168.

Utilizing Patient-Centered Approaches in PAH: The Expanding Role of Pharmacists
The Right Ventricle in PAH

- RV pressure/volume overload
- RV failure

*Progressive structural changes in the RV due to poor adaptation to increasing PVR*

Cross-section

French Registry: Kaplan-Meier Survival Estimates in Combined PAH Population vs. NIH-predicted

![Survival Graph]

No. at risk: All patients 56 69 98 113 120 127 133


REVEAL: Observed 1-year Survival From Time of Enrollment According to Predicted Risk Strata

![Survival Graph]

No. at risk:
- Low 1374 1351 1303
- Average 665 640 596
- Mod. high 280 260 243
- High 295 263 225
- Very high 102 72 49


Utilizing Patient-Centered Approaches in PAH: The Expanding Role of Pharmacists
Patient Presentation: Nonspecific Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>50</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20</td>
</tr>
<tr>
<td>Near syncope/syncope</td>
<td>15</td>
</tr>
<tr>
<td>Chest pain</td>
<td>10</td>
</tr>
<tr>
<td>Palpitations</td>
<td>10</td>
</tr>
<tr>
<td>Edema</td>
<td>5</td>
</tr>
</tbody>
</table>

Median Time From Symptom Onset to Diagnosis

- NIH Registry (1981 to 1985): 1.3 years
- REVEAL Registry (2006 to 2007): 1.1 years

Clinical Case: Meet Jane

- 37-year-old woman, previously healthy
- Delivered second child 14 mo previously
- Limited exercise tolerance since delivery, attributed to weight gain
- Dyspnea while playing with older child; syncope while walking up an incline

Jane’s Initial Symptoms

- Currently has dyspnea with mild exertion, walks slowly in store
- Exertional light-headedness
- Atypical chest pain
- Occasional palpitations
- Lower extremity edema

Jane’s Additional History

- PMH: 2 children, 4 yr and 14 mo
  - IBS: diet-controlled
- Meds: none
- Allergies: contrast dye
- FH: PAH in a paternal aunt, CAD, DM, HTN
- SH: rare ETOH, o/w unremarkable

Jane: Physical Exam

- HR 90 bpm; BP 130/68 mm Hg; Wt 190 lb; Ht 5’ 4”
- JVP ~15 cm, reduced carotid upstrokes
- Clear lungs
- Palpable RV heave, RRR, NL S, loud P₂, III/VI, TR murmur
- 2+ LE edema

Is There a Reason to Suspect PAH?

**Clinical Presentation**

<table>
<thead>
<tr>
<th>History</th>
<th>Exam (PH)</th>
<th>Exam (RV Failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea (86%)</td>
<td>Loud P₂ (listen at apex)</td>
<td>JVD; increased A wave, V wave;</td>
</tr>
<tr>
<td>Fatigue (27%)</td>
<td>RV lift (left parasternal – fingertips)</td>
<td>hepatojugular reflex</td>
</tr>
<tr>
<td>Chest pain (22%)</td>
<td>RV S₃, S₄</td>
<td>Pulsatile liver</td>
</tr>
<tr>
<td>Edema (22%)</td>
<td>Systolic murmur (TR; inspiratory augmentation)</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Syncope (17%)</td>
<td>Early systolic click</td>
<td>Edema</td>
</tr>
<tr>
<td>Dizziness (15%)</td>
<td>Midsystolic ejection murmur</td>
<td>Ascites</td>
</tr>
<tr>
<td>Cough (14%)</td>
<td>Diastolic murmur (PR)</td>
<td>Low BP, low PP, cool extremities</td>
</tr>
<tr>
<td>Palpitations (13%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pivotal Tests: RHC

- Refer to a PH center if:
  - accurate tracings (especially PCWP) are difficult to obtain
  - vasoreactivity testing is not available

Vasoreactivity Testing

- Patients with pre-capillary PH
- Inhaled nitric oxide is recommended (typically protocolized at PH centers)
- Decrease in mPAP by ≥10 mm Hg and
- Decrease of mPAP to <40 mm Hg and
- No significant decrease in CO

**Jane: Right Heart Catheterization**

<table>
<thead>
<tr>
<th></th>
<th>1/29/07 Baseline</th>
<th>Nitric Oxide 20 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mm Hg)</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>93/40, mean 63</td>
<td>93/46, mean 64</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>52.9</td>
<td>58.3</td>
</tr>
<tr>
<td>Femoral artery</td>
<td>91.4</td>
<td>91.7</td>
</tr>
<tr>
<td>Cardiac output / Cardiac index (L/min) Fick</td>
<td>2.5/1.3</td>
<td>2.88/1.52</td>
</tr>
<tr>
<td>PVR (Wood units) Fick</td>
<td>21.2</td>
<td>15.2</td>
</tr>
</tbody>
</table>

LVEDP, left ventricular end diastolic pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure

PAH Treatment Goals

- Fewer/less severe symptoms
- Improve exercise capacity
  - 6MWD
  - WHO functional classification
- Improve hemodynamics
- Prevent clinical worsening
  - escalation of therapy
  - hospitalization
  - lung transplantation
  - death
- Improve quality of life
- Improve survival

6MWD, six-minute walk distance
Initial Therapy: Making the Right Decision

- Severity of disease
- Patient preference
- Trying to weigh the data
- When "comparing" trials, examine:
  - objective baseline characteristics of participants (age, functional class, 6MWD, hemodynamics)
  - outcome measures (6MWD, time to clinical worsening)

French Registry: Kaplan-Meier Survival Estimates According to Baseline NYHA Functional Class


French Registry: Kaplan-Meier Survival Estimates According to Baseline 6MWD


Utilizing Patient-Centered Approaches in PAH: The Expanding Role of Pharmacists
Hemodynamic Abnormalities and Prognosis (IPAH)

Median survival (months)

Mean PAP
Mean RAP
Mean CI

Survival Rates of Patients With PAH, Stratified by PVR and RVEF at Baseline

PVR
RVEF
RVEF and PVR

Plasma BNP as a Prognostic Indicator in Patients With IPAH

By multivariate analysis, higher BNP at follow-up (RR=25.880, p=0.0243) was an independent predictor of mortality.

### PAH Determinants of Risk

<table>
<thead>
<tr>
<th>LOWER RISK</th>
<th>DETERMINANTS OF RISK</th>
<th>HIGHER RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Gradual</td>
<td>Progression of symptoms</td>
<td>Rapid</td>
</tr>
<tr>
<td>II, III</td>
<td>WHO class</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt;400 m)</td>
<td>6MWD</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Peak VO2 &gt;10.4 mL/kg/min</td>
<td>CPET</td>
<td>Peak VO2 &lt;10.4 mL/kg/min</td>
</tr>
<tr>
<td>Minimal RV dysfunction</td>
<td>Echocardiography</td>
<td>Pericardial effusion, significant RV enlargement/dysfunction; RA enlargement</td>
</tr>
<tr>
<td>RAP &lt;10 mm Hg; CI &gt;2.5 L/min/m²</td>
<td>Hemodynamics</td>
<td>RAP &gt;20 mm Hg; CI &lt;2.0 L/min/m²</td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>BNP</td>
<td>Significantly elevated</td>
</tr>
</tbody>
</table>

CPET, cardiopulmonary exercise testing; BNP, B-type natriuretic peptide

### 5th World Symposium on PH Goals of Therapy: Setting the Bar Higher

**Functional Class**
- I or II

**Hemodynamics**
- Normalization of RV function (RAP <8 mm Hg and CI >2.5–3.0 L/min/m²)

**Echocardiography/ MRI**
- Normal/near normal RV size and function

**BNP level**
- ‘Normal’

**6MWD**
- 380–440 m, may not be aggressive enough

**CPET**
- Peak VO2 >15 mL/kg/min
- VE/VCO₂ @ AT <45


### 5th World Symposium on PH: 2013 PAH Treatment Algorithm

- Supervised exercise training (I-A)
- Psycho-social support (I-C)
- Avoid strenuous physical activity (I-C)
- Avoid pregnancy (I-C)
- Influenza and pneumococcal immunization (I-C)

- General measures and supportive therapy

- Expert Referral (I-C)

- Oral anticoagulants:
  - IPAH, heritable PAH, and PAH due to anorexigen (IIb-C)
  - APAH (Ib-C)
  - Diuretics (I-C)
  - Oxygen (I-C)
  - Digoxin (Ib-C)

Chronic Adjuvant Therapies in PAH

**Digoxin**
- Variable inotropic effect and use
- No long-term data; need to balance unproven benefits with known risks

**Oxygen**
- Use to prevent hypoxic vasoconstriction
- Consider exercise, sleep, altitude
- Aim for target saturation >90%
- May not correct hypoxia with shunt


### Chronic Adjuvant Treatment

**Diuretics**
- Needed by most patients
- Hypotension not a contraindication
- Renal function and electrolytes must be monitored closely

**Anticoagulation**
- Recommended in IPAH
- Observational data only
- Need to balance unproven benefits with known risks
- INR goal 1.5–2.5

---

**Other Management Issues**

- Encourage exercise and activity within the limits of disease and ability to maintain $O_2$ levels
- Consider enrollment in a pulmonary rehabilitation program
- Immunizations
- Contraception
- Psycho-social support; role of support groups

---

Utilizing Patient-Centered Approaches in PAH: The Expanding Role of Pharmacists
5th World Symposium on PH: 2013 PAH Treatment Algorithm

- Supervised exercise training (I-A)
- Psycho-social support (I-C)
- Avoid strenuous physical activity (I-C)
- Avoid pregnancy (I-C)
- Influenza and pneumococcal immunization (I-C)
- General measures and supportive therapy
  - Expert referral (I-C)
  - Acute vasoactivity test (I-C for IPAH) (IIb-C for APAH)
- Oral anticoagulants: – IPAH, heritable PAH, and PAH due to anorexigens (IIb-C)
  – APAH (IIb-C)
  – Diuretics (I-C)
  – Oxygen (I-C)
  – Digoxin (IIb-C)

Vasodilator Challenge

- iNO (most commonly) at 40 ppm
- Positive if:
  - drop in mPAP >10 mm Hg to a mean <40 mm Hg
  - no decline in CO/CI
  - no rise in PCWP
- Suggests response to calcium channel blocker
- Caveats:
  - only indicated for IPAH patients
  - 50% lose vasoreactivity over time

Why Is It Important? Survival in IPAH

Long-term CCB Responders

<table>
<thead>
<tr>
<th>Years</th>
<th>Subjects at risk, n</th>
<th>Long-term CCB responders</th>
<th>Long-term CCB failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>38</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>2-4</td>
<td>33</td>
<td>0.80</td>
<td>0.20</td>
</tr>
<tr>
<td>4-6</td>
<td>30</td>
<td>0.60</td>
<td>0.40</td>
</tr>
<tr>
<td>6-8</td>
<td>22</td>
<td>0.40</td>
<td>0.60</td>
</tr>
<tr>
<td>8-10</td>
<td>13</td>
<td>0.20</td>
<td>0.80</td>
</tr>
<tr>
<td>10-12</td>
<td>8</td>
<td>0.10</td>
<td>0.90</td>
</tr>
<tr>
<td>12-14</td>
<td>3</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>14-16</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-18</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18+</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Long-term Response to CCBs in Non-idiopathic PAH


How Do I Treat a Responder?

- High-dose calcium channel blockers
  - nifedipine 180–240 mg/d
  - diltiazem 720–960 mg/d
  - amlodipine 20–30 mg/d

- Must re-catheterize after 3–6 months of therapy to assess sustained response
  - 50% will lose vasoreactivity over time
  - Treat as other PAH patients

Changes in PAH Trials Over Time

Given the changes in PAH treatment, short-term assessment of 6MWD may not be the best PAH trial endpoint in 2012.

PAH Drug Classes

- Prostacyclin Derivatives
- Endothelin Receptor Antagonists
- Soluble Guanylate Cyclase Stimulators
- Phosphodiesterase Inhibitors
- Calcium Channel Blockers

5th World Symposium on PH: 2013 PAH Treatment Algorithm

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>WHO FC II</th>
<th>WHO FC III</th>
<th>WHO FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia A or B</td>
<td>Ambrisentan, Bosentan, Macitentan, Riociguat, Sildenafil, Tadalafil</td>
<td>Ambrisentan, Bosentan, Epoprostenol IV, Iloprost inh and IV*</td>
<td>Epoprostenol IV</td>
</tr>
<tr>
<td>Ia C</td>
<td>Iloprost IV*, Treprostinil IV</td>
<td>Ambrisentan, Bosentan, Iloprost inh and IV*</td>
<td>Macitentan, Riociguat, Sildenafil, Tadalafil, Treprostinil SC, inh</td>
</tr>
<tr>
<td>Ib B</td>
<td>Beraprost*</td>
<td>Initial Combination Therapy</td>
<td>Initial Combination Therapy</td>
</tr>
<tr>
<td>Ib C</td>
<td>Initial Combination Therapy</td>
<td>Initial Combination Therapy</td>
<td></td>
</tr>
</tbody>
</table>

In patients with IPAH, which agent(s) have been shown to increase survival in a randomized clinical trial?

1. Calcium channel blockers
2. Epoprostenol
3. Bosentan
4. Treprostinil
5. All of the above
Which of the following agents would you choose to treat Jane’s PAH?

1. Amlodipine
2. Epoprostenol
3. Bosentan
4. Riociguat
5. Tadalafil

Jane: Initial Management

- Admitted to hospital following RHC
- IV diuresis
- IV epoprostenol initiation

Therapeutic Targets for PAH

Prostacyclin General Characteristics

- Often considered gold standard for advanced disease
- Unique administration devices
- Interruptions must be avoided
- Differ in stability, half-life, and method of delivery
- Available only through restricted drug distribution system (RDDS)
- Titrated to response and tolerability
- **High-risk, error-prone medications**

Prostacyclin Analogues: IV and SQ Formulations

<table>
<thead>
<tr>
<th>Prostacyclin Analogue</th>
<th>Administration</th>
<th>FC</th>
<th>Dose</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol Sodium</td>
<td>Continuous IV infusion via infusion pump. Requires tunneled CVC. Epoprostenol requires use of ice packs. Requires reconstitution.</td>
<td>III, IV</td>
<td>Initiated at 2 ng/kg/min and titrated based on response. Ongoing: 1-2 ng/kg/min q1-2 wk.</td>
<td>CHF due to severe LVD. Avoid abrupt withdrawals or interruption in infusion: may result in rebound PH or death.</td>
</tr>
<tr>
<td>Remodulin® 1mg/mL, 2mg/mL, 5mg/mL, 10mg/mL in 20mL vials</td>
<td>Continuous IV or SubQ infusion via infusion pump. IV requires tunneled CVC.</td>
<td>II-IV</td>
<td>Initiated at 1.25 ng/kg/min and titrated based on response. Ongoing: 1.25 ng/kg/min every week or as tolerated</td>
<td>Initiated in controlled setting. Monitor for signs of BSI.</td>
</tr>
</tbody>
</table>
**Prostacyclin Analogues: Pivotal Trials for Inhaled and Oral Formulations**

<table>
<thead>
<tr>
<th>Study Name / Drug</th>
<th>N / Etiol / Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
</table>
| AIR Inhaled iloprost vs placebo | III-IV | Double-blind, 12-week | • Composite end point  
• Symptoms  
• Hemodynamics |
| TRIUMPH 1 Inhaled treprostinil vs placebo§ | PAH III-IV* | Double-blind, 12-week on background oral Rx | • 6MWD |
| FREEDOM-M Oral treprostinil vs placebo | PAH II-III | Double-blind, placebo-controlled 12-week | • 6MWD |

*Approved for class III only. Included background therapy with ERA or PDE-5I.


Jane’s epoprostenol titrations are underway. Which of the following is a potential dose-related effect of epoprostenol?

1. Urticaria
2. Hypotension
3. Anemia
4. Constipation
Management of Prostacyclin-Related Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Management Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>OTC analgesics, Tramadol, opiates if severe</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Loperamide, Lomotil, adjust titrations</td>
</tr>
<tr>
<td>Nausea</td>
<td>Ondansetron or other anti-emetics, food (oral formulation)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Adjust antihypertensive drugs, diuretics. Adjust titrations</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Adjust titrations</td>
</tr>
<tr>
<td>Jaw Pain</td>
<td>Start first meal with bland food, “exercise jaw”</td>
</tr>
<tr>
<td>Leg Pain</td>
<td>Elevate legs, gabapentin, pregabalin, amitriptyline, other pain meds</td>
</tr>
<tr>
<td>Flushing</td>
<td>Adjust titrations</td>
</tr>
</tbody>
</table>

Management of SC Prostacyclin Effects

- Topical Agents
- Systemic Management
  - H1 and H2 blockers
  - OTC analgesics, opioids if severe
  - GABA analogs
  - Others
- Non-pharmacologic management
  - Catheter dwell times
  - Catheter type
  - Dry insertion
- Other strategies:
  - Pre-medicate
  - Rapid titration
  - Increase concentration

Endothelin Receptor Antagonists: General Characteristics

- ERAs antagonize ET\textsubscript{A} receptors\textsuperscript{*}
- Available only through limited distribution
- Risk Evaluation and Mitigation Strategies (REMS)
  - Inpatient and outpatient requirements
- Oral formulation

\textsuperscript{*} Bosentan and macitentan are dual ET\textsubscript{A} and ET\textsubscript{B} receptor antagonist.
Endothelin Receptor Antagonists: Pivotal Trials

<table>
<thead>
<tr>
<th>Study Name Drug</th>
<th>N Etiology Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BREATHE-1</td>
<td>PAH II, III, IV</td>
<td>Double-blind 16-week</td>
<td>· 6MWD</td>
</tr>
<tr>
<td>Oral bosentan² vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EARLY</td>
<td>PAH II</td>
<td>Double-blind 6-month</td>
<td>Delay clinical worsening</td>
</tr>
<tr>
<td>Oral bosentan vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIES-1&amp;2</td>
<td>PAH II, III</td>
<td>Double-blind 12-week</td>
<td>· 6MWD</td>
</tr>
<tr>
<td>Oral ambrisentan³ vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SERAPHIN</td>
<td>PAH II, III</td>
<td>Double-blind Event-driven morbidity/mortality</td>
<td>· Delay disease progression</td>
</tr>
<tr>
<td>Oral macitentan² vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Endothelin Receptor Antagonists: Pivotal Trials

Guanylate Cyclase Stimulator

- Novel mechanism
- First non-WHO Group 1 approved indication
- Available only through RDDS
- Risk Evaluation and Mitigation Strategies (REMS) for teratogenicity
- Requires blood pressure monitoring and titration

Utilizing Patient-Centered Approaches in PAH: The Expanding Role of Pharmacists
### sGC Stimulator Pivotal Trials

<table>
<thead>
<tr>
<th>Study Name Drug</th>
<th>N Etiology Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATENT-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral riociguat* vs placebo</td>
<td>278 PAH I-IV</td>
<td>Double-blind 12-week</td>
<td>• 6MWD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hemodynamics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Delay clinical worsening</td>
</tr>
<tr>
<td>CHEST-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral riociguat vs placebo</td>
<td>261 CTEPH I-IV</td>
<td>Double-blind 16-week</td>
<td>• 6MWD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hemodynamics</td>
</tr>
</tbody>
</table>

*Riociguat = Adempas®. Approved for WHO Group 1: persistent CTEPH (WHO Group 4) after surgical treatment, or inoperable CTEPH; titrated to maximum 2.5 mg po tid.


### Sildenafil

<table>
<thead>
<tr>
<th>How Supplied</th>
<th>REMS</th>
<th>Properties</th>
<th>CI/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>generic Revatio® 28 mg tablets</td>
<td>n/a</td>
<td>T½ &lt;4 hours Metabolized by CYP3A4 and CYP2C9 (minor)</td>
<td>Caution with organic nitrates. Increased mortality risk in peds. Caution with SCD, PVOD. Post-marketing AE: NAION</td>
</tr>
<tr>
<td>Revatio® 10 mg/12.5 mL soln for injection</td>
<td>FC</td>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td>Powder for suspension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Mostly II-III</td>
<td>Oral: 20 mg TID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inj.: 10 mg TID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Tadalafil

<table>
<thead>
<tr>
<th>How Supplied</th>
<th>REMS</th>
<th>Properties</th>
<th>CI/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adcirca® 20 mg tablets</td>
<td>n/a</td>
<td>T½ ~35 hrs Metabolized by CYP3A4</td>
<td>Caution with organic nitrates</td>
</tr>
<tr>
<td></td>
<td>FC</td>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>II-III</td>
<td>40mg daily</td>
<td></td>
</tr>
<tr>
<td>Oral tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### PDE-5 Inhibitor Pivotal Trials

<table>
<thead>
<tr>
<th>Study Name Drug</th>
<th>N Etiology Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUPER-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral sildenafil* vs placebo</td>
<td>278 PAH I-IV</td>
<td>Double-blind 12-week</td>
<td>• 6MWD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hemodynamics</td>
</tr>
<tr>
<td>PHIRST-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral tadalafil ¹ vs placebo</td>
<td>405 PAH I-IV</td>
<td>Double-blind 16-week</td>
<td>• 6MWD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Delay clinical worsening</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hemodynamics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HRQoL</td>
</tr>
</tbody>
</table>

*Sildenafil = Revatio®. Approved for FC II-III. 20 mg po tid.
¹Tadalafil = Adcirca®. Approved for FC I-IV. 40 mg po qd.

Utilizing Patient-Centered Approaches in PAH: The Expanding Role of Pharmacists
Management of Oral Therapy Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Management Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>OTC analgesics, Tramadol, opiates if severe</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>Add or adjust diuretics, salt and fluid restrictions</td>
</tr>
<tr>
<td>Anemia</td>
<td>Periodic CBC monitoring Reduce dose or discontinue drug</td>
</tr>
<tr>
<td>Hemorrhagic events</td>
<td>Caution with anticoagulants Monitor for bleeding/bruising</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>PRN OTC agents if infrequent H2 blocker or PPI</td>
</tr>
<tr>
<td>Nausea</td>
<td>Anti-emetics</td>
</tr>
<tr>
<td>Hypotension, Dizziness</td>
<td>Monitor BP in between dose titrations Adjust antihypertensive drugs, diuretics Reduce dose or hold titration if needed (riociguat)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>PRN OTC agents if infrequent H2 blocker or PPI</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>Saline nasal spray</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>Obtain negative pregnancy test monthly for women of reproductive age Contraception mandatory</td>
</tr>
<tr>
<td>Elevated LFT's</td>
<td>Monitor LFT's monthly (bosentan) Reduce dose or discontinue drug</td>
</tr>
</tbody>
</table>

Recently Completed or Ongoing Clinical Trials of Combination Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Current Therapy</th>
<th>Added Therapy</th>
<th>Patients (n)</th>
<th>Study Duration</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMBITION</td>
<td>Ambrisentan/tadalafil/combo</td>
<td>Combo vs mono</td>
<td>500</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>104</td>
<td>12 weeks</td>
<td>6MWD</td>
</tr>
<tr>
<td>COMPASS-2</td>
<td>Sildenafil</td>
<td>Bosentan</td>
<td>250</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
</tr>
<tr>
<td>ATPAHSS</td>
<td>Ambrisentan/tadalafil/combo</td>
<td>Combo vs mono</td>
<td>63</td>
<td>36 weeks</td>
<td>RV mass/PVR</td>
</tr>
<tr>
<td>GRIPHON</td>
<td>ERA, PDE5i, or both</td>
<td>Selexipag</td>
<td>1156</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
</tr>
<tr>
<td>Ikaria</td>
<td>≥1 current therapies</td>
<td>Inhaled NO</td>
<td>78</td>
<td>16 weeks</td>
<td>PVR</td>
</tr>
<tr>
<td>FREEDOM-Ev</td>
<td>PDE5i or ERA</td>
<td>Oral treprostinil</td>
<td>858</td>
<td>24 weeks (6MWD)/event driven</td>
<td>6MWD/ 1st clinical worsening event</td>
</tr>
</tbody>
</table>

Investigational Oral Prostacyclin Therapy: Time to First Morbidity or Mortality Event—GRIPHON

**AMBITION: Effect of Ambrisentan Plus Tadalafil Versus Monotherapy on Clinical Worsening**


**Combination Therapy Caveats**

- Experience evolving
- Most data from ‘add-on’ - ? De novo? Order?
- More drugs available
  - more options
  - more ways to get it wrong
- More questions than answers
- Costs/expenditures; third-party hurdles

**Transitioning Therapy**

**Rationale**

- Recurrent bacteremia
- Clinical deterioration
- Profound improvement (benefits vs. risks)
- Intolerable side effects
- Limitations with therapy management
- Lifestyle, patient preference

**Potential concerns**

- Intermittent vs. continuous dosing of prostacyclin
- Dose limitations with inhaled therapy
- Patient compliance
- Follow-up
- Patient selection

**Types**

- Transitioning parenteral prostacyclins
  - Titration
  - Rapid
- Transitioning inhaled prostacyclins
- Parenteral to or from inhaled prostacyclin
- Prostacyclin to oral
# Targeted Therapies: Use With Caution

<table>
<thead>
<tr>
<th>Other drugs</th>
<th>Co-Morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Multiple anti-hypertensive drugs</td>
<td>• Liver or renal impairment</td>
</tr>
<tr>
<td>• Anti-platelet or anti-coagulants</td>
<td>• Congestive heart failure</td>
</tr>
<tr>
<td>• Sympathomimetic agents</td>
<td>• Depression</td>
</tr>
<tr>
<td>• Strong inhibitors or inducers of specific CYP P450 enzymes</td>
<td>• Cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>• Substance abuse disorder</td>
</tr>
<tr>
<td></td>
<td>• Dexterity/mobility impairment</td>
</tr>
<tr>
<td></td>
<td>• Significant hypotension</td>
</tr>
<tr>
<td></td>
<td>• Immunosuppression</td>
</tr>
</tbody>
</table>

# Transitions in Care

- Know your institution’s policies and procedures
  - Be prepared and prioritize patient safety
  - Discharge planning
  - Contacting PAH specialists and specialty pharmacy
- Special enrollments and medication access process
  - REMS requirements
- Be familiar with significant drug interactions and AEs
- Engage the patient and caregiver, they are very well-trained and knowledgeable
  - Most patients carry backup meds/devices with them

# Opportunities for Pharmacists

- Comprehensive medication reconciliation and history
- Education and training on targeted therapies and devices
- Participation in therapy selection and therapeutic alternatives
- Policies and procedure development
- Coordinate medication access
- Program enrollment for REMS or restricted distribution therapies
- Ongoing safe-use monitoring
- Dose verification, order entry and drug interactions
- Health maintenance
- Medication titration and adverse effect management
- Resource for other healthcare providers
Jane: Return Visit in May & September

- Significantly improved
- No limitations
- Functional class I
- Meds
  - epoprostenol 30 ng/kg/min
  - warfarin
  - furosemide 20 mg
  - KCl 10 mEq qd

Jane: Follow-up Physical Exam

- HR 80; BP 103/59 mm Hg; Wt 144.8 lb
- JVP 6 cm, carotid upstrokes NL
- Clear lungs
- Palpable RV heave, NL S, loud P₂, II/VI
  - TR murmur
- No LE edema

Jane: 6MWD

- 222 m: 99–96% in January
- 486 m: 99–97% in May
- 556 m: 99–97% in September
Summary

- PAH-specific therapies promote vasodilation, leading to reduction in pulmonary vascular resistance and improved RV function
- Therapies are highly individualized and require a multi-disciplinary team of healthcare providers with specialized training
- Selection of initial therapy largely depends upon severity of disease at diagnosis
  - low-risk patients can be treated with oral agents
  - high-risk patients require parenteral prostacyclins
- Lack of improvement or worsening of parameters should trigger escalation of therapy
- There are a number of challenges associated with these complex therapies
- Pharmacists are an important part of the PAH therapy team and many opportunities are available to promote improved patient care
### INITIAL THERAPY WITH PAH-APPROVED DRUGS

**Red:** Morbidity and mortality as primary end point in randomized controlled study or reduction in all-cause mortality (prospectively defined)

Level of evidence based on WHO-FC of majority of patients of studies

<table>
<thead>
<tr>
<th>Evidence</th>
<th>WHO FC II</th>
<th>WHO FC III</th>
<th>WHO FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>I A or B</td>
<td>Ambrisentan, Bosentan&lt;br&gt;Macitentan&lt;br&gt;Rioigigat&lt;br&gt;Sildenafil&lt;br&gt;Tadalafil</td>
<td>•Ambrisentan, Bosentan, Epoprostenol IV&lt;br&gt;•Iloprost inh&lt;br&gt;•Macitentan&lt;br&gt;•Rioigigat&lt;br&gt;Sildenafil&lt;br&gt;Tadalafil&lt;br&gt;Treprostinil SC, inh</td>
<td>•Epoprostenol IV</td>
</tr>
<tr>
<td>Ila C</td>
<td>Iloprost IV*, Treprostinil IV</td>
<td>•Ambrisentan, Bosentan, Iloprost inh and IV*&lt;br&gt;•Macitentan&lt;br&gt;•Rioigigat&lt;br&gt;Sildenafil, Tadalafil&lt;br&gt;Treprostinil SC, IV, Inh*</td>
<td></td>
</tr>
<tr>
<td>Iib B</td>
<td>Beraprost*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iib C</td>
<td>Initial Combination Therapy</td>
<td>Initial Combination Therapy</td>
<td></td>
</tr>
</tbody>
</table>


### Therapeutic Targets for PAH

- **Endothelin Pathway**
  - Pre-proendothelin → Proendothelin → Endothelin-1
  - Endothelin receptor A
  - Endothelin receptor B
  - Endothelin-receptor antagonists

- **Nitric Oxide Pathway**
  - L-arginine → L-citrulline
  - Guanylate Cyclase
  - cGMP
  - Phosphodiesterase type 5
  - sGC agonists
  - Exogenous nitric oxide
  - Phosphodiesterase type 5 inhibitor

- **Prostacyclin Pathway**
  - Prostaglandin I2 (PGI2)
  - Prostacyclin (PGI2)
  - cAMP
  - Prostacyclin derivatives
  - Vasodilation and antiproliferation

**Prostacyclin Analogues: IV and SQ Formulations**

<table>
<thead>
<tr>
<th>How Supplied</th>
<th>Administration</th>
<th>FC</th>
<th>Dose</th>
<th>Properties</th>
<th>CI/P/Misc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol Sodium</td>
<td>Continuous IV infusion via infusion pump &amp; tunneled CVC</td>
<td>III, IV</td>
<td>Initiated at 2 ng/kg/min and titrated based on response. Ongoing: 1-2 ng/kg/min q1-2 wk.</td>
<td>T ½ &lt;6 min. Temp and light sensitive. Reconstituted stability dependent on formulation. Rapidly hydrolyzed in the blood.</td>
<td>CHF due to severe LVD. Avoid abrupt withdrawals or interruption in infusion: may result in rebound PH or death.</td>
</tr>
<tr>
<td>Generic, Flolan®, or Veletri® 0.5mg, 1.5mg</td>
<td>Continuous IV or SubQ infusion via infusion pump &amp; tunneled CVC</td>
<td>II-IV</td>
<td>Initiated at 1.25 ng/kg/min and titrated based on response. Ongoing: 1.25 ng/kg/min every week or as tolerated</td>
<td>T ½ ~4 hours. Metabolized by CYP 2C8. Diluted: 48-hour infusion duration. Undiluted: 72-hour infusion duration.</td>
<td>Initiated in controlled setting. Monitor for signs of BSI.</td>
</tr>
</tbody>
</table>

**Oral and Inhaled Prostacyclins**

<table>
<thead>
<tr>
<th>How Supplied</th>
<th>Administration</th>
<th>FC</th>
<th>Dose</th>
<th>Properties</th>
<th>CI/P/Misc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iloprost</td>
<td>Intermittent inhalation via dedicated inhalation device</td>
<td>III, IV</td>
<td>2.5 mcg once, then 5 mcg per dose if tolerated for 6 to 9 x/day</td>
<td>T ½ ~20 to 30 min. Caution if underlying lung disease or symptomatic hypotension. Bronchospasm Store at RT Discard unused solution One ampule used per treatment session (20 mcg/mL = 5 mcg dose only!)</td>
<td></td>
</tr>
<tr>
<td>Ventavis® 10 mcg/mL and 20 mcg/mL unit dose ampules</td>
<td>Intermittent inhalation via dedicated inhalation device</td>
<td>III</td>
<td>3 breaths QID, titrated to goal 9 breaths QID</td>
<td>T ½ ~4 hours. Metabolized by CYP 2C8. One inhaled ampule provides multiple doses/day Once opened: discard remaining solution after 24 hours, protect ampules from light during storage</td>
<td></td>
</tr>
<tr>
<td>Treprostinil Syntelis® for inhalation 0.6 mg/mL in 2.9 mL ampules</td>
<td>Oral extended release osmotic tablets</td>
<td>II, III</td>
<td>Initial: 0.25 mg BID or 0.125 mg TID, titrate every 3 to 4 days</td>
<td>T ½ ~4 hours. Metabolized by CYP 2C8. Food increases bioavailability</td>
<td>Abrupt discontinuation, Diverticulitis Severe hepatic impairment Avoid alcohol</td>
</tr>
<tr>
<td>Treprostinil Orenitram® 0.125 mg, 0.25 mg, 1 mg and 2.5 mg ER tablets</td>
<td>Oral extended release osmotic tablets</td>
<td>II, III</td>
<td>Initial: 0.25 mg BID or 0.125 mg TID, titrate every 3 to 4 days</td>
<td>T ½ ~4 hours. Metabolized by CYP 2C8. Food increases bioavailability</td>
<td>Abrupt discontinuation, Diverticulitis Severe hepatic impairment Avoid alcohol</td>
</tr>
</tbody>
</table>

---


Orenitram® (treprostinil) US Prescribing Information. United Therapeutics Corp. October 2014.


<table>
<thead>
<tr>
<th>Bosentan</th>
<th>How Supplied</th>
<th>REMS</th>
<th>Properties</th>
<th>CI/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracleer® 62.5 mg, 125 mg tablets</td>
<td>Teratogenicity, liver toxicity. Must enroll in Tracleer REMS Program</td>
<td>T½ ~5 hours Metabolized and strong inducer of CYP3A4 and CYP2C9; possibly CYP2C19; Caution with drug intx.</td>
<td>Ci: Pregnancy and use of cyclosporine or glyburide. Caution with liver disease.</td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td>II-IV</td>
<td>FC Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral tablets. Can be dissolved into soln.</td>
<td>Initial: 62.5 mg BID x 4 weeks, then increase to 125 mg BID thereafter if tolerated and wt &gt;40 kg.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ambrisentan</th>
<th>How Supplied</th>
<th>REMS</th>
<th>Properties</th>
<th>CI/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letairis® 5 mg, 10 mg tablets</td>
<td>Teratogenicity. FRP must enroll in Letairis REMS Program</td>
<td>T½ up to ~15 hours Metabolized by CYP3A4 and CYP2C19, substrate of P-glyco-protein</td>
<td>Ci: pregnancy and IPF. Caution with anemia, fluid retention, PVOD.</td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td>II-III</td>
<td>FC Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Macitentan</th>
<th>How Supplied</th>
<th>REMS</th>
<th>Properties</th>
<th>CI/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opsumit® 10 mg tablets</td>
<td>Teratogenicity. FRP must enroll in Opsumit REMS Program</td>
<td>T½ ~16 hrs (48 hrs for active metabolite) Metabolized by CYP3A4 and CYP2C19; active metabolite contributes ~40% of activity.</td>
<td>Ci: Pregnancy Caution with anemia, liver disease.</td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td>Mostly II-III</td>
<td>FC Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sildenafil</th>
<th>How Supplied</th>
<th>REMS</th>
<th>Properties</th>
<th>CI/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>generic Revatio® 20 mg tablets</td>
<td>n/a</td>
<td>T½ ~4 hours Metabolized by CYP3A4 and CYP2C9 (minor)</td>
<td>Ci: use with organic nitrates. Increased mortality risk in peds. Caution with SCD, PVOD. Post marketing AE: NAION</td>
<td></td>
</tr>
<tr>
<td>Revatio® 10 mg/12.5 mL soln for injection Powder for suspension</td>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td>Mostly II-III</td>
<td>Oral: 20 mg TID Inj.: 10 mg TID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral tablets or suspension. Solution for injection used for NPO.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tadalafil</th>
<th>How Supplied</th>
<th>REMS</th>
<th>Properties</th>
<th>CI/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adcirca® 20 mg tablets</td>
<td>n/a</td>
<td>T½ ~35 hrs Metabolized by CYP3A4</td>
<td>Ci: use with organic nitrates Caution with SCD, PVOD.</td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td>II-III</td>
<td>FC Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral tablets</td>
<td></td>
<td>40mg daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>