WHAT IS PAH?

“Pulmonary arterial hypertension is a chronic, progressive disease of the small pulmonary arteries, characterized by vascular remodeling that results in increased pulmonary vascular resistance and pulmonary arterial pressure, and ultimately leads to right ventricular failure and death.”


DEFINITION

Right Heart Catheterization
- Mean PAP ≥ 25 mm Hg
- PAWP ≤ 15 mm Hg
- PVR > 3 WU

Wood units (WU) = Calculated pulmonary vascular pressure
PAP - PAWP/CO
Normal = < 3 Wood Units

Hoeppe, et al. JACC. 2013;62:d42-d50

STATISTICS

- Age
  - REVEAL (2006-) 50 ± 17
  - European COMPERA Registry (2007-2011) 65 ± 15

- Prevalence
  - 10-52 cases/million

2013 NICE CLASSIFICATION

1. Primary Arterial Hypertension
- Idiopathic
- Heritable
- Drug and Toxic induced
  - Associated with:
    - Connective Tissue Disease
    - HIV
    - Portal Hypertension
    - Congential Heart Disease
    - Schistosomiasis

2. - PH due to Left Heart Disease
- Systolic or Diastolic Dysfunction
- Valvular Disease
- Congential/Acquired Left Heart flow tract obstruction and Cardiomyopathies

3. - PH due to Lung Disease/ Hypoxia
- COPD
- ILD
- Mixed restrictive and obstructive
- Sleep-Disordered Breathing
- Alveolar Hypoventilation
- Chronic Exposure High Altitude
- Developmental Lung Disease


2013 NICE CLASSIFICATION

<table>
<thead>
<tr>
<th>6- Chronic Thromboembolic PH</th>
<th>PH with unclear mechanisms</th>
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<tbody>
<tr>
<td>Hematologic Disorders;</td>
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<tr>
<td>• Chronic hemolytic anemia</td>
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<tr>
<td>• Myeloproliferative disorders</td>
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<tr>
<td>• Splenectomy</td>
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<td>Systemic Disorders;</td>
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<tr>
<td>• Sarcoidosis</td>
<td></td>
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<tr>
<td>• Pulmonary Histiocytosis</td>
<td></td>
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<tr>
<td>• Lymphangioleiomyomatosis</td>
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<tr>
<td>Metabolic Disorders;</td>
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<tr>
<td>• Glycogen storage disease</td>
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<tr>
<td>• Gaucher’s disease</td>
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<tr>
<td>• Thyroid disorders</td>
<td></td>
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<tr>
<td>Others</td>
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</table>

CTEPH


WHO FUNCTIONAL CLASSIFICATION

I Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause dyspnea or fatigue, chest pain, or near syncope.

II Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

III Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

IV Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.


PHARMACOTHERAPY

GOAL OF THERAPY

- Improved 6MWD (6 minute walking distance)
- Long-term morbidity and mortality
- Time to clinical worsening
  - All-cause mortality
  - Unscheduled hospitalization
  - Clinical Progression
- Improved WHO Functional Classification (WHO FC)
- Better quality of life

CONVENTIONAL THERAPY

- Calcium Channel Blockers
- Anti-coagulation
- Oxygen
- Diuretics
- Digoxin

ENDOTHELIN PATHWAY

Endothelin Pathway

Prostanoid Pathway

Nitrergic pathway

NO synthase

Nitric oxide

Endothelial cells

Endothelins

www.phassociation.org
ENDOTHELIN ANTAGONIST

BOSENTAN - TRACLEER®

ET-1 A/ETB receptor types A & B antagonists

- Dosing
  - 62.5mg-125mg PO BID
- Elimination half life
  - 5 hours
- Dose adjustment
  - Severe hepatic impairment - not recommended for use
- Boxed warning
  - Hepatotoxicity, Teratogenicity
- REMS program - TAP (Tracleer Access Program)

REMS PROGRAM

- The Food and Drug Administration Amendments Act of 2007 gave FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks.

ENDOTHELIN ANTAGONIST

BOSENTAN - TRACLEER®

Tracleer Assistance Program (TAP)

1. Prior to RX, discuss risks of treatment including hepatotoxicity and teratogenicity
2. Order and review liver function tests (ALT/AST/bilirubin) and confirm that female patients of childbearing potential are not pregnant
3. Agree to order and monitor monthly liver function and, if applicable, pregnancy tests
4. Educate and counsel females of childbearing potential on the need to use reliable methods of contraception during treatment with Tracleer and for 1 month after treatment discontinuation

ENDOTHELIN ANTAGONIST

BOSENTAN - TRACLEER®

- Contraindications
  - Pregnancy
  - Cyclosporine or glyburide
- Adverse Drug Reactions
  - Headache, Edema, Chest Pain, Syncope, Sinusitis, Flushing, Hypotension, Anemia
- Drug Interactions
  - DC 36 hrs prior to start ritonavir, wait 10 days before restart
  - Decreased serum concentration contraceptives
  - Reduced concentration of CYP3A4 substrates

ENDOTHELIN ANTAGONIST

BOSENTAN - TRACLEER®

- Specialty Pharmacy
  - Limited distribution. Cannot be purchased at a local pharmacy.
  - It must be prescribed by a physician through the Tracleer® Access Program (TAP) and insurance approval must be obtained prior to starting therapy. TAP will forward the request to a specialty pharmacy.
  - Costs ~$7000 per month

http://www.tracleerrems.com/
**ENDOTHELIN ANTAGONIST AMBRISENTAN - LETAIRIS®**

ET-1 A/ETB receptor types A & B antagonists

- **Dosing**
  - 5mg-10mg PO daily
- **Elimination half life**
  - 9 hours
- **Dose adjustment**
  - No dose adjustment needed for renal or hepatic impairment

https://www.letairis.com/

**ENDOTHELIN ANTAGONIST AMBRISENTAN - LETAIRIS®**

ET-1 A/ETB receptor types A & B antagonists

- **Boxed warning**
  - Embryo-fetal toxicity
- **REMS program** - LEAP program Females only (Letairis Education and Access Program)
  - Monthly pregnancy test, use of appropriate birth control while taking Letairis, and for 1 month after stopping Letairis

**ENDOTHELIN ANTAGONIST AMBRISENTAN - LETAIRIS®**

- **Contraindications**
  - Pregnancy
  - IPF
- **Adverse Drug Reactions**
  - Peripheral edema, nasal congestion, sinusitis, flushing
- **Drug Interactions**
  - Decreased dose to 5mg/day if cyclosporine

**ENDOTHELIN ANTAGONIST MACITENTAN - OPSUMIT®**

ET-1 A/ETB receptor types A & B antagonists

- **Dosing**
  - 10mg PO daily
- **Elimination half life**
  - 16 hours
- **Dose adjustment**
  - No dose adjustment needed for renal or hepatic impairment

http://opsumit.com/

**ENDOTHELIN ANTAGONIST MACITENTAN - OPSUMIT®**

ET-1 A/ETB receptor types A & B antagonists

- **Boxed warning**
  - Embryo-fetal toxicity
- **REMS program** - Opsumit Risk Evaluation and Mitigation Strategy Program - females only
  - Monthly pregnancy test, use of appropriate birth control while taking Opsumit, and for 1 month after stopping
**ENDOTHELIN ANTAGONIST**
**MACITENTAN - OPSUMIT®**

- **Contraindications**
  - Pregnancy

- **Adverse Drug Reactions**
  - Anemia, Nasopharyngitis, Bronchitis, Headache, Influenza, UTI

- **Drug Interactions**
  - Avoid with strong CYP3A4 inducers (rifampin) and CYP3A4 inhibitors (ketoconazole, itraconazole)

- **Specialty Pharmacy**
  - Limited distribution. For women, must be prescribed by a physician through the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS) Program because of the risk to embryo or fetus if the woman becomes pregnant. Insurance approval must be obtained prior to starting therapy and OPSUMIT REMS will forward the request to an authorized specialty pharmacy.

- **Costs**
  - ~$7200 per month

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**PHOSPHODIESTERASE INHIBITORS**
**SILDENAFIL - REVATIO®**

- **PDE-5 inhibitor**

- **Dosing**
  - 5mg or 20 mg PO TID
  - 2.5mg or 10 mg IV TID

- **Elimination half life**
  - 4 hours

- **Dose adjustment**
  - No dose adjustment

- **Boxed warning**
  - NA

- **REMS program**
  - NA

- **Contraindications**
  - Hypersensitivity
  - Concurrent use of any nitrates

- **Adverse Drug Reactions**
  - Flushing, Headache, Dyspepsia, Visual disturbances, Epistaxis

- **Drug Interactions**
  - Nitrates
  - Concomitant use with ritonavir and other strong CYP3A4 inhibitors not recommended

- **Costs**
  - ~$125 (PO generic) per month
  - Prior to generic, ~$1200-$4000 per month
PHOSPHODIESTERASE INHIBITORS  
TADALAFIL - ADCIRCA®

- **PDE-5 inhibitor**
- **Dosing**
  - 40 mg PO daily
- **Elimination half life**
  - 35 hours
- **Boxed warning** - NA
- **REMS program** - NA

http://www.adcirca.com

PHOSPHODIESTERASE INHIBITORS  
TADALAFIL - ADCIRCA®

- **Dose adjustment**
  - Renal: for CrCl 31-80 ml/min initiate 20 mg PO daily, increase to 40 mg if CrCl ≤ 30 ml/min
  - Avoid use in ESRD on HD
  - Hepatic
    - Mild to moderate - use with caution, consider 20 mg PO daily
    - Severe - avoid use

- **Rems program** - NA

http://www.adcirca.com

PHOSPHODIESTERASE INHIBITORS  
TADALAFIL - ADCIRCA®

- **Contraindications**
  - Concurrent use of any nitrates
- **Adverse Drug Reactions**
  - Flushing, Headache, Dyspepsia, Myalgia, Back/Extremity pain, RTI, Nasopharyngitis
- **Drug Interactions**
  - Nitrates or other PDE inhibitor contraindicated
  - Monitor BP with co-administration antihypertensives
  - Concomitant use with ritonavir, other strong CYP3A4 inhibitors or inducers not recommended

www.pha.org

GUANYLATE CYCLASE STIMULATOR  
RIOCI GUAT - ADEMPAS®

- **Dosing for CTEPH & PAH**
  - 0.5-2.5 mg PO TID
- **Elimination half life**
  - 12 hours
- **Dose adjustment**
  - Renal:
    - Not recommended for CrCl < 15 ml/min
    - Not recommended for ESRD on HD

Adempas® http://www.adempas-us.com/
GUANYLATE CYCLASE STIMULATOR
RIOCIGUAT - ADEMPAS®

- **Clinical and Lab Criteria**
  
<table>
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<tr>
<th></th>
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<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>MILD to moderate (grade 1 or 2)</td>
<td>Severe (grade 3 or 4)</td>
</tr>
<tr>
<td>Acute</td>
<td>None</td>
<td>MILD to moderate (diastolic range not defined)</td>
<td>Severe (diastolic range not defined)</td>
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<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 3</td>
<td>3-5</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
<td>2.8-3.5</td>
<td>≤ 2.8</td>
</tr>
<tr>
<td>Prothrombin time (seconds prolonged)</td>
<td>&lt; 1.7</td>
<td>1.7-2.3</td>
<td>&gt; 2.3</td>
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</tbody>
</table>

Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)
- Class A: < 5 points (mild liver disease)
- Class B: ≥ 7 to 9 points (moderately severe liver disease)
- Class C: ≥ 10 to 19 points (severe liver disease)

GUANYLATE CYCLASE STIMULATOR
RIOCIGUAT (ADEMPAS®)

- **Dose Adjustment**
  - Hepatic: not recommended for Child-Pugh Class C
  - Hypotension: by 0.5 mg TID
  - Concomitant use of CYP3A4 and PGP/BRCP inhibitors; consider start dosage 0.5 mg TID
  - Smokers: titrate dosage to >2.5 mg TID, consider dose with smoking cessation

GUANYLATE CYCLASE STIMULATOR
RIOCIGUAT (ADEMPAS®)

- **Boxed warning** - Embryo-fetal toxicity
- **REMS program** - Adempas REMS Program
  - Exclude pregnancy before the start of treatment
  - Monthly during treatment
  - 1 month after stopping treatment
- **Contraindications**
  - Pregnancy
  - Nitrates
  - Concomitant administration with PDE inhibitors

GUANYLATE CYCLASE STIMULATOR
RIOCIGUAT (ADEMPAS®)

- **Adverse Drug Reactions**
  - Peripheral edema, Headache, Dyspepsia, Anemia, N & V, Diarrhea
- **Drug Interactions**
  - Monitor BP when used with other antihypertensives
  - Concomitant use of CYP3A inhibitors or PBP/BRCP; start lower dose 0.5 mg TID
  - Strong CYP3A inducers may ↓ exposure
  - Do not take antacids within 1 hour

GUANYLATE CYCLASE STIMULATOR
RIOCIGUAT (ADEMPAS®)

- **Specialty Pharmacy**
  - Must be prescribed by a physician, and insurance approval must be obtained prior to starting therapy. It is carried by specialty pharmacies, including Accredo Health Inc., CVS Caremark and Walgreen Specialty
- **Costs**
  - ~$8000 per month

PROSTANOIDS
EPOPROSTENOL (FLOLAN®, VELETRI®)

- **Prostacyclin**
  - Strong vascular vasodilator
  - Inhibits platelet aggregation
- **1st known therapy 1995**
- **Dosing**
  - 2-40 ng/kg/min IV continuous (maximum dose not defined)

1 mg = 1,000,000 (1 million) nanograms
1 mg = 1,000 microgram

www.pha.org
**PROSTANOIDS**

**EPOPROSTENOL (FLOLAN®, VELETRI®)**

- Elimination half life: 6 minutes
- Dose adjustment: No dose adjustment for renal or hepatic impairment
- Boxed warning: NA
- REMS program: NA
- Contraindications:
  - Hypersensitivity
  - Chronic use in Left Ventricular Systolic Dysfunction
  - Edema after initial dosing

**Adverse Drug Reactions**

- Tachycardia, Flushing, Hypotension, Dizziness, Headache, Anxiety, N & V, Diarrhea, Infection, Skin/Jaw/Musculoskeletal pain, skin ulcer, Chills/Fever/Flu-Like Symptoms

**Drug Interactions**

- Concomitant use of antihypertensives and other vasodilators
- Concomitant use of anticoagulants
- Concomitant use of Digoxin (↑ serum concentration)

**Specialty Pharmacy**

- Limited distribution medication
- The drug is provided directly from specialty pharmacies (Accredo Health Group, Inc., and CVS Caremark) that provide a team of clinical pharmacists and nurses. They assist with all aspects involved in the long-term usage of epoprostenol, including insurance issues, education on pump function and central line care, providing pumps and supplies and technical troubleshooting with 24-hour hotlines.

**Costs**

- Flolan: $5700 per month
- Veletri: $6100 per month

**PROSTANOIDS**

**TREPROSTINIL (REMODULIN®, TYVASO®, ORENITRAM®)**

- Prostacyclin
  - Direct vasodilator pulmonary and systemic arterial vasculature
  - Inhibits platelet aggregation
- Dosing:
  - IV & SQ: 0.625-40 ng/kg/min IV continuous (maximum dose not defined)
  - Inhaled: 6-18 mcg (3-9 breaths) inhaled QID
  - PO: Start 0.25 mg PO BID then titrate q 3-4 days by 0.25 mg q 12 hours to treatment effect (maximum dose is determined by tolerability)
- Elimination half life: 4 hours

- Dose adjustment
  - No dose adjustment for renal impairment
  - Hepatic
    - Inhalation: titrate slowly
    - IV & SQ: use with caution and titrate slowly
    - PO:
      - Mild - 0.125 mg every 12 hours every 3-4 days
      - Moderate - avoid use
      - Severe - contraindicated
- Boxed warning: NA
- REMS program: NA
**PROSTANOIDS**

**TREPROSTINIL**

- **Contraindications**
  - Oral: Severe hepatic impairment (Child-Pugh Class 3)

- **Adverse Drug Reactions**
  - Flushing, Headache, Skin rash, Diarrhea, Nausea, Pain at injection site, Infusion site Rx, Limb pain (PO), Jaw pain, Cough and throat pain (Inhalation)

- **Drug Interactions**
  - Coadministration with CYP2C8 inducers ↓, inhibitors ↑ plasma levels of IV, SQ, and PO
  - Concomitant use of antihypertensives and other vasodilators
  - Concomitant use of anticoagulants

**PROSTANOIDS**

**TREPROSTINIL (REMODULIN®)**

- Limited distribution medication
- Costs
  - $19,000 per month

**PROSTANOIDS**

**TREPROSTINIL (REMODULIN®)**

- Special considerations:
  - Stable at room temperature
  - SQ can be converted to IV if needed
  - OR, procedures, etc
  - Longer half-life
  - However, if stopped can lead to severe rebound symptoms, even death
  - IV: Need central venous access; Hickman, Tunneled line, PICC
  - Commitment from patient and family

**PROSTANOIDS**

**TREPROSTINIL (TYVASO®)**

- Inhaled treprostinil is a limited distribution medication
- Specialized nebulizer
  - 4 sessions, 4 hours apart
  - Initial: 3 breaths per session
  - Maintenance: ↑3 breaths (18 ng) 1-2 weeks until target 9 breaths (54 ng) per session
- Costs
  - Inhaled: $13,000 per month

**PROSTANOIDS**

**TREPROSTINIL (ORENITRAM®)**

- Limited distribution. Insurance approval must be obtained prior to starting therapy and OSUMIT REMS will forward the request to an authorized specialty pharmacy
- Costs
  - PO: $10,000 per month

**PROSTANOIDS**

**ILOPROST - VENTAVIS®**

- Dose adjustment
  - No dose adjustment for renal
  - Hepatic impairment Child-Pugh Class B or C: ↑ dosing interval every 3-4 hours based on response
  - Boxed warning - NA
  - REMS program - NA

Inhaled: $13,000 per month

http://www.4ventavis.com/
PROSTANOIDS

ILOPROST (VENTAVIS®)

- Contraindications
  - NA
- Adverse Drug Reactions
  - Flushing, Hypotension, Headache, Nausea, Jaw pain, Cough, Flu like symptoms, Trismus
- Drug Interactions
  - Concomitant use of antihypertensives and other vasodilators
  - Concomitant use of anticoagulants

Limited distribution medication.
Specialized Nebulizer
- Initial: 2.5 mcg 6-9 x’s day
- Maintenance: ↑ 5 mcg 6-9 x’s day
- Concentration
  - 10 mcg/ml
  - 20 mcg/ml for patients with extended treatment times
- Costs
  - ~$15,000 per month

http://www.4ventavis.com

INITIAL THERAPY:
WHO GROUP I - PAH (NON-REACTIVE)

<table>
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<tr>
<th>Level</th>
<th>Evidence</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
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<tbody>
<tr>
<td>I</td>
<td>A or B</td>
<td>Ambrisentan</td>
<td>Bosentan</td>
<td>Macitentan</td>
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<tr>
<td>Ia</td>
<td>C</td>
<td>Ambrisentan</td>
<td>Bosentan</td>
<td>Epoprostenol</td>
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<tr>
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<td></td>
<td>Macitentan</td>
<td>Riociguat</td>
<td>Macitentan</td>
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</tbody>
</table>


WHO GROUP II, III, IV

- Treat the underlying cause
- No RCT to support WHO Group I therapies in Group 2 & 3 PH

2- PH due to Left Heart Disease
- Systolic HF
  - strict volume control
  - neuro hormonal (ACE) modulators
- Diastolic HF
  - Strict volume control
  - BP control
- L sided Valvular Dysfunction
  - Surgical repair/replacement

3- PH due to Lung Disease/ Hypoxia
- COPD
- anti-inflammatory therapies
- bronchodilators
- Sleep-Disordered Breathing
  - CRAP at night
  - Hypoxia
  - O2

4- Chronic Thromboembolic PH
- Referred to surgical center with experience in pulmonary thromboendarterectomy (PTE)

Choosing Wisely
Five Things Physicians and Patients Should Question

SELEXIPAG (UPTRAVI®)
- Oral, selective non-prostanoid IP receptor agonist
- Elimination half life
  - Selexipag 0.8-2.5 hours, active metabolites 6.2-13.5 hours
- Dosing
  - Starting dose 200 mcg BID
  - Increase by 200 mcg BID at weekly intervals to the highest tolerated dose up to 1600 mcg BID
  - Missing dose
    - < 6 hours, give dose
    - > 6 hours, hold until next dose
    - If dose missed ≥ 3 days, restart at lower dose and titrate up
  - Better tolerated with food
  - Do not crush

SELEXIPAG (UPTRAVI®)
- Dose adjustment
  - Child-Pugh class B - QD dosing recommended, Avoid in severe hepatic disease
  - No clinical experience with HD or GFR < 15 ml/min
  - Avoid concomitant use CYP2C8 inhibitors: increase exposure
  - Discontinue in nursing mothers or stop breastfeeding
- Warning and Precautions
  - Do not use in patients with confirmed Pulmonary Veno-Occlusive Disease
  - Pulmonary Edema

SELEXIPAG (UPTRAVI®)
- Other Considerations
  - Change in hgb < 10 g/dL was reported in 8.6% patients vs 5% placebo
  - Change in TSH up to -0.3 MU/L vs no change in placebo
- Adverse Drug Reactions
  - HA, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, flushing,
  - Overdose
    - Isolated cases reported with mild, transient nausea.
    - HD likely ineffective; protein bound
- Costs
  - ~ up to $20,000 per month

DELLIVERY
DEVICE IMPLANTABLE INTRAVASCULAR CATHETER TO DELIVER REMODULIN IN PAH
- Multicenter, prospective, single arm, non-randomized, open label
  - Up to 70 subjects at up to 10 US sites, followed for at least 12 months
  - Patients currently treated with the approved intravenous (IV) infusion route of delivery of Remodulin Injection for PAH
  - Ongoing, not recruiting

McLaughlin, et al. JACC. 2015;65(10-S)

NITRIC OXIDE

- Inhaled Nitric Oxide/INOpulse DS for Pulmonary Arterial Hypertension (PAH)
- Phase 2, Placebo Controlled, Double-Blind, Randomized, Clinical Study to Determine Safety, Tolerability and Efficacy of Pulsed, Inhaled Nitric Oxide (iNO) Versus Placebo as Add-on Therapy in Symptomatic Subjects with Pulmonary Arterial Hypertension (PAH)
- Phase 3 clinical trials for INOpulse for PAH in the second half of 2015

http://www.bellerophon.com/pipeline/inopulse-technology

"I like the dreams of the future better than the history of the past."
~Thomas Jefferson

CCHS PAH Team

Thank You
mseckel@christianacare.org