Update on the Management of Pulmonary Hypertension

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Disclosures

- None

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Treatment (Conventional/Supportive)

- Immunize
- Oxygen
- Low sodium diet
- Diuretics
- Digoxin
- Cardiopulmonary rehabilitation
- Anticoagulation?

Treatment (Targeted Therapies)

- Calcium Channel Blockers (CCB)
- Prostacyclin Analogs (PGI_2)
- Prostacylin IP Receptor Agonist
- Endothelin Receptor Antagonists (ERA)
- Phosphodiesterase 5 Inhibitors (PDE-5)
- Soluble Guanylate Cyclase Stimulator (sGC)
- Nitric Oxide (NO)
- Surgical/Device

Treatment: Mechanisms

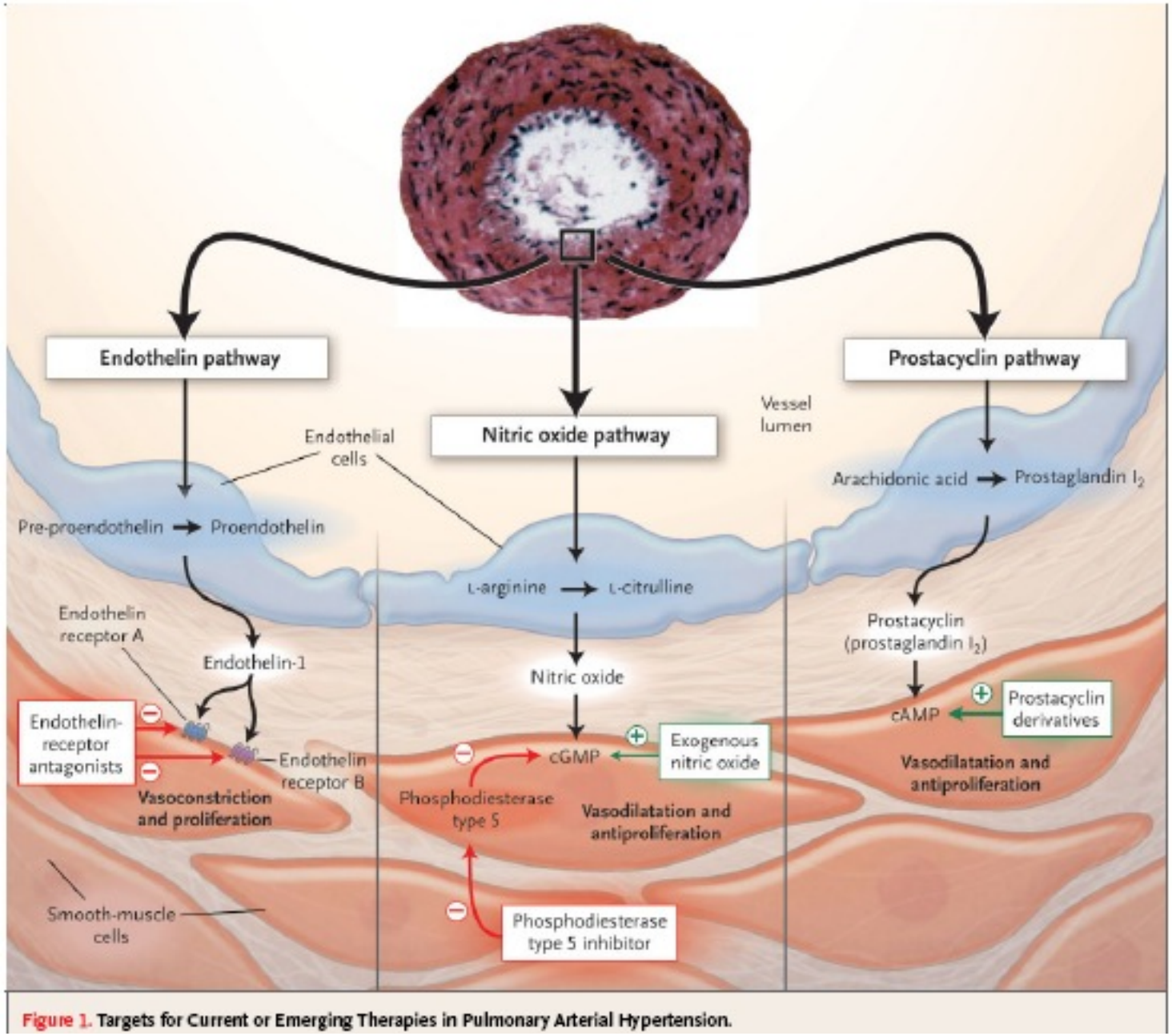

Figure 1. Targets for Current or Emerging Therapies in Pulmonary Arterial Hypertension.

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Humbert M et al. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004; 1425-36.

Calcium Channel Blockers (IPAH)

- Vasoreactivity (Right Heart Catheterization)
  - NO 10-40 ppm for 10 min
  - Response ↓ mPAP 10 mm Hg and to a value < 40 mm Hg
- 13% respond and 50% lose CCB vasoreactivity in one year
- Dihydropyridines preferred unless tachycardia or Afib
  - Nifedipine (extended release)120-240 mg/day
  - Amlodipine 2.5-20 mg/day
  - Diltiazem 240-720 mg/day

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DiPiro JT. Pulmonary arterial hypertension. *Pharmacotherapy: a pathophysiologic approach, 9th Ed* 2014; 429-440.

Prostacyclin Analogs

- Parenteral
  - Epoprostenol (Flolan, Veletri)
  - Treprostenil (Remodulin)
- Inhaled
  - Iloprost (Ventavis)
  - Treprostenil (Tyvaso)
- Oral
  - Treprostinil (Orenitram)

Epoprostenol Flolan/Veletri (Parenteral)

- MOA: strong vasodilator all vascular beds and endogenous inhibitor of platelet aggregation.
- PK: Rapidly hydrolyzed to inactive and minimally active metabolites with an elimination half-life of 6 minutes
- Dosing: 2 ng/kg/min IV continuous infusion increasing based on patient tolerance by 1-2 ng/kg/min every 15 minutes until dose-limiting ADR.
  - Usual optimal dose monotherapy (4-6 weeks): 25-40 ng/kg/minute
  - Maximum dose adults based on adverse effects (higher doses in children)
- ADRs: Flushing, nausea/vomiting, flu-like syndrome (chills/fever), headache, jaw pain, hypotension, chest pain, anxiety

LexiComp Flolan Prescribing Information 2014

Epoprostenol (Flolan)

- Epoprostenol diluted to concentrations of 3,000 ng/ml, 5,000 ng/ml, 10,000 ng/ml, 15,000 ng/ml
- Flolan diluent required
- Stability reconstituted: 8 hours at room temperature, 24 hours in ice pack, 48 hours in refrigerator
- Protect from light
- Infuse central line preferred through 0.2 micron inline filter
- REQUIRES BACK UP CASETTE!!

0.5 mg and 1.5 mg vials

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LexiComp Flolan Prescribing Information 2014

Epoprostenol (Veletri)

- Epoprostenol diluted to concentrations of 3,000 ng/ml, 5,000 ng/ml, 10,000 ng/ml, 15,000 ng/ml, 30,000 ng/ml
- Sodium chloride 0.9% diluent
- Stable for 48 hours at room temperature
- Protect from light
- Infuse central line preferred through 0.2 micron inline filter
- REQUIRES BACK UP CASETTE!!

0.5 mg and 1.5 mg vials

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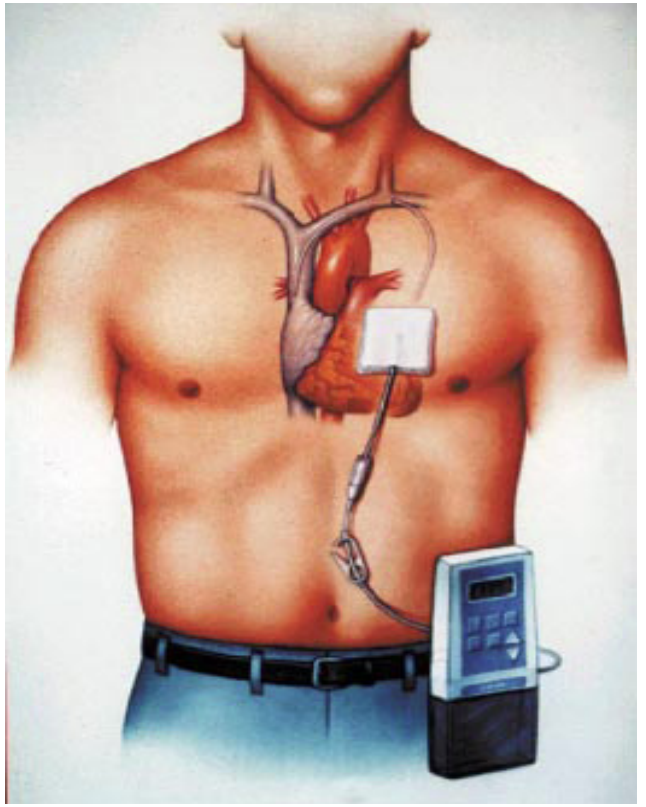
LexiComp Veletri Prescribing Information 2014

CADD Pump Infusion



Epoprostenol Clinical Data

- Improved exercise tolerance (6 minute walk), hemodynamic, survival

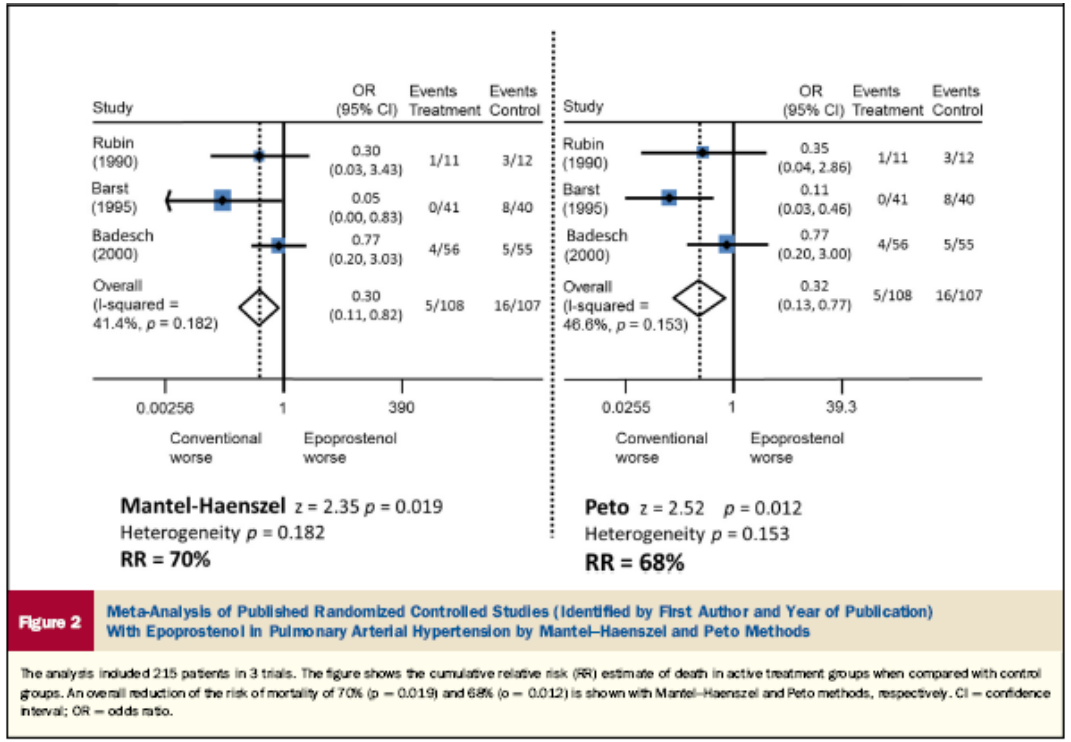


Figure 2 Meta-Analysis of Published Randomized Controlled Studies (Identified by First Author and Year of Publication) With Epoprostenol in Pulmonary Arterial Hypertension by Mantel–Haenszel and Peto Methods

The analysis included 215 patients in 3 trials. The figure shows the cumulative relative risk (RR) estimate of death in active treatment groups when compared with control groups. An overall reduction of the risk of mortality of 70% (p = 0.019) and 68% (p = 0.012) is shown with Mantel–Haenszel and Peto methods, respectively. CI = confidence interval; OR = odds ratio.

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Galie N. Updated treatment algorithm of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62: D60-72).

Treprostinil (Remodulin) Parenteral

- MOA: strong vasodilator all vascular beds and endogenous inhibitor of platelet aggregation.
- PK:
  - A: SQ/IV
  - D: 14L
  - M/E: Hepatic CYP2C8 inactive metabolites; terminal half-life 4 hours
- Dosing(adverse effects and hemodynamic improvement)
  - 1.25 ng/kg/min IV/SC continuous infusion (reduce to 0.625 ng/kg/min with intolerance or BL hepatic impairment)
  - ↑ 1.25 ng/kg/min per week for first month
  - ↑ 2.5 ng/kg/min per week
  - Target doses >13 ng/kg/min associated with improved survival (max around 40 ng/kg/min)
- Transition from epoprostenol 24-48 hours in hospital

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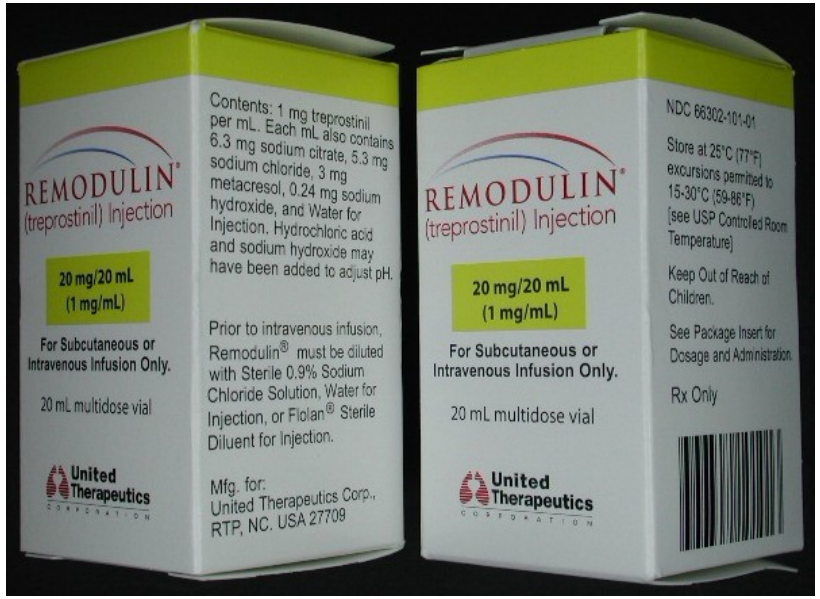
LexiComp Remodulin Prescribing Information 2014

Treprostenil (Remodulin)

- Remodulin SC undiluted stable for 72 hours at room temp
- Remodulin IV diluted in 50-100 ml of diluent stable for 48 hours at room temp
- Protect from light
- Infuse central line preferred through 0.2 micron inline filter
- REQUIRES BACK UP CASETTE!!



20 mg, 50 mg, 100 mg, 200 mg vials

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Remodulin Prescribing Information 2014

Bloodstream Infections in Patients Given Treatment With Intravenous Prostanoids

Alexander J. Kallen, MD, MPH; Edith Lederman, MD, MPH; Alexandra Balaji, PhD; Ingrid Trevino, DVM, MPH; Emily E. Petersen, BS; Rivka Shoulson, DVM; Lisa Saiman, MD, MPH; Evelyn M. Horn, MD; Mardi Gomberg-Maitland, MD, MSc; Robyn J. Barst, MD; Arjun Srinivasan, MD

OBJECTIVE. In September 2006, the Centers for Disease Control and Prevention was notified of cases of gram-negative bloodstream infection (BSI) occurring among outpatients who received an intravenous formulation of the prostanoid treprostinil. An investigation was conducted to determine rates of prostanoid-associated BSI in this patient population and possible risk factors for infection.

METHODS. We performed a retrospective cohort study of patients who had received intravenous formulations of at least 1 of the 2 approved prostanoids (epoprostenol and treprostinil) from January 1, 2004, through late 2006. Chart reviews were conducted at 2 large centers for pulmonary arterial hypertension, and a survey of infection control practices was conducted at 1 center.

RESULTS. A total of 224 patients were given intravenous prostanoid treatment, corresponding to 146,093 treatment-days during the study period. Overall, there were 0.55 cases of BSI and 0.18 cases of BSI due to gram-negative organisms per 1,000 treatment-days. BSI rates were higher for patients who received intravenous treprostinil than for patients who received intravenous epoprostenol (1.13 vs. 0.42 BSIs per 1,000 treatment-days; $P < .001$), as were rates of BSI due to gram-negative organisms (0.81 vs. 0.04 BSIs per 1,000 treatment-days; $P < .001$). Adjusted hazard ratios for all BSIs and for BSIs due to gram-negative organisms were higher among patients given treatment with intravenous treprostinil. The survey identified no significant differences in medication-related infection control practices.

CONCLUSION. At 2 centers, BSI due to gram-negative pathogens was more common than previously reported and was more frequent among patients given treatment with intravenous treprostinil than among patients given treatment with intravenous epoprostenol. Whether similar results would be found at other centers for pulmonary arterial hypertension warrants further investigation. This investigation underscores the importance of surveillance and evaluation of healthcare-related adverse events in patients given treatment primarily as outpatients.

Infect Control Hosp Epidemiol 2008; 29:342-349

Treprosinil SC

CHEST Original Research
PULMONARY HYPERTENSION

Transition From IV Epoprostenol to Subcutaneous Treprostinil in Pulmonary Arterial Hypertension*

A Controlled Trial

Melvyn Rubenfire, MD†; Vallerie V. McLaughlin, MD, FCCP; Roblee P. Allen, MD, FCCP; Greg Elliott, MD; Myung H. Park, MD; Michael Wade, PhD; and Robert Schilz, DO, PhD

Background: **We determined the relative efficacy of subcutaneous (SC) treprostinil in stable World Health Organization class II and III patients transitioned from IV epoprostenol.**
Methods: **This was an 8-week, multicenter, randomized study in which patients were transitioned from IV epoprostenol to SC treprostinil or placebo over a period of up to 14 days and monitored carefully during and after the transition period for signs of deterioration. Patients with clinical deterioration were returned promptly to epoprostenol. Placebo or SC treprostinil doses were titrated in response to symptoms. Time to adjudicated clinical deterioration was compared between treatment groups, and exercise capacity, symptoms of disease, and safety were assessed throughout the study.**
Results: **Twenty-two patients were enrolled and completed the study. Seven of 8 patients (88%) withdrawn to placebo had clinical deterioration, while only 1 of 14 patients (7%) withdrawn to SC treprostinil had clinical deterioration ($p = 0.00023$ based on a treatment comparison of time to deterioration). Analyses of exercise capacity and symptoms strongly supported the efficacy of SC treprostinil in epoprostenol-treated patients. Adverse events consisted of painful infusion site reactions and anticipated prostacyclin side effects.**
Conclusions: **SC treprostinil is effective in pulmonary arterial hypertension and prevents clinical deterioration and maintains functional status in patients transitioned from epoprostenol.**
(CHEST 2007; 132:757–763)

Key words: prostacyclin; pulmonary hypertension; withdrawal trial

Abbreviations: AE = adverse event; PAH = pulmonary arterial hypertension; SC = subcutaneous; WHO = World Health Organization

Table 4—*Most Frequent AEs in the Treprostinil Group

AEs	Treprostinil (n = 14)	Placebo (n = 8)
Infusion site pain	13 (93)	3 (38)
Nausea	6 (43)	6 (75)
Headache	6 (43)	5 (63)
Diarrhea	7 (50)	3 (38)
Infusion site erythema	10 (71)	0 (0)
Dizziness	6 (43)	3 (38)
Flushing	6 (43)	3 (38)
Upper respiratory infection	5 (36)	1 (13)
Vomiting	4 (29)	1 (13)
Pain in jaw	4 (29)	1 (13)
Abdominal distension	3 (21)	1 (13)
Pain in extremity	3 (21)	1 (13)
Dyspnea	2 (14)	1 (13)
Infusion site induration	3 (21)	0 (0)
Infusion site swelling	3 (21)	0 (0)
Injection site pruritis	2 (14)	0 (0)
Pyrexia	2 (14)	0 (0)
Syncope	2 (14)	0 (0)
Infusion site warmth	2 (14)	0 (0)

*Data are presented as No. (%).

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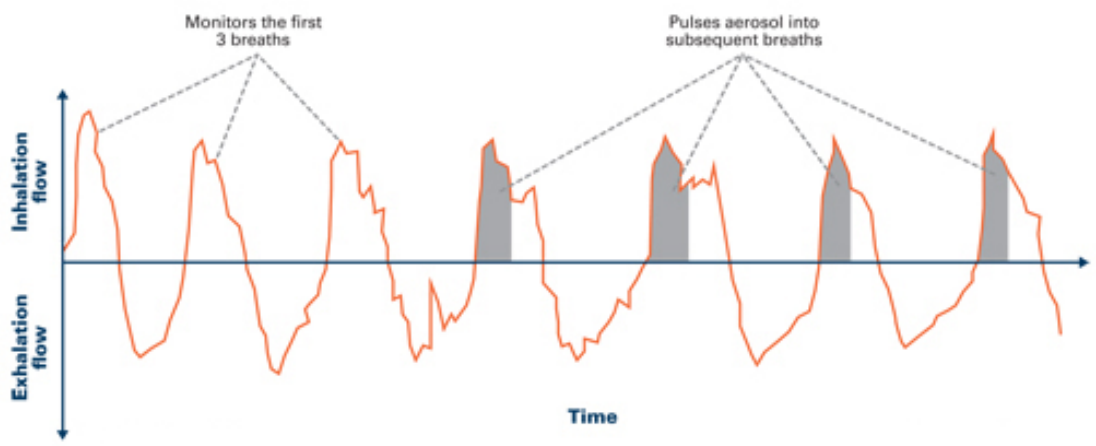
Rubenfire M et al. *Chest* 2007; 132: 757-763.

Inhaled Prostenoids (Iloprost)

- Iloprost (Ventavis)
  - WHO I (labeled) – WHO III
  - Dosing (10 mcg/1 ml vial, 20 mcg/1 ml vial): 2.5 mcg-5 mcg 6-9 times/ day while awake (no more frequently than every 2 hours)
  - Use the I-neb AAD Nebulizer



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Ventavis Prescribing Information 2014

Inhaled Prostenoids (Treprostinil)

- Treprosinil (Tyvaso)
- WHO I (labeled) –WHO III (most patients with background of bosentan or sildenafil)
- Dosing (0.6 mg/ml 2.9 ml vial): 3 inhalations using Tyvaso Inhalation System (6 mcg/inhalation) every 4 hours 4 times daily. ↑ by 3 inhalations every 1-2 weeks to target maintenance dose of 9 inhalations 4 times daily.
- Entire days therapy placed in device in the morning.

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Tyvaso Prescribing Information 2014

Oral Prostenoid Treprostinil Diolamine (Orenitram)

0.125 mg , 0.25 mg , 1 mg, and 2.5 mg tablets

- Treprostinil Extended Release Tablets (Orenitram)
- PK:
  - A: F=0.17, Cmax = 5 hours
  - D: PPB 96%, Vd = 14 L
  - M/E: Hepatic CYP 2C8 inactive metabolites,
    T1/2 = 4 hours, OROS drug delivery system
- Dosing(Available in 0.125, 0.25, 1, and 2.5 mg tablets):
  - 0.25 mg oral twice daily (0.125 mg in mild hepatic impairment or on CYP 2C8 inhibitor gemfibrozil)
  - ↑ 0.25-0.50 mg twice daily every 3-4 days as tolerated
  - Maximum dose by tolerability or 16 mg bid in trials
- ADRS: headache, nausea, diarrhea

Orenitram Freedom-C2

Patients: N = 310 (73% WHO III) PAH patients on ERA(17%), PDE5 (43%) or ET + PDE5 (40%) for 90 days.

Design: Randomized (Blocks), PC, Trial 1:1 16 week trial

Study Dose: Orenitram 0.25 mg bid to maximum tolerability every 3 days to week 4, after that 0.5 mg increases could be performed up to the maximum of 16 mg bid

Primary Outcome: Change in 6 MWD from BL

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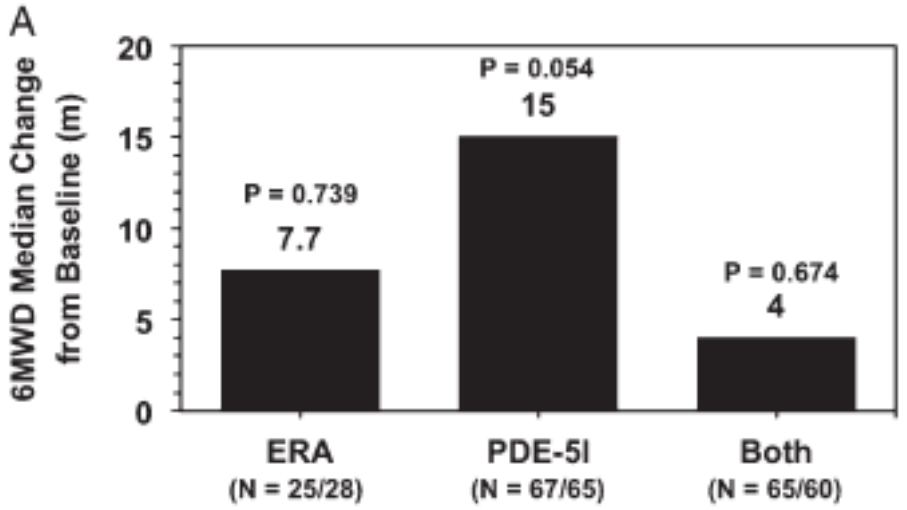
Tapson VF et al. Freedom-C2. *Chest* 2013; 144: 952-58.

Orenitram FREEDOM-C2 Results

- 16% Orenitram discontinued d/t adverse effect compared to 10% placebo
- Mean maximum dose orenitram at week 16 = 3.1 ± 1.9 mg bid



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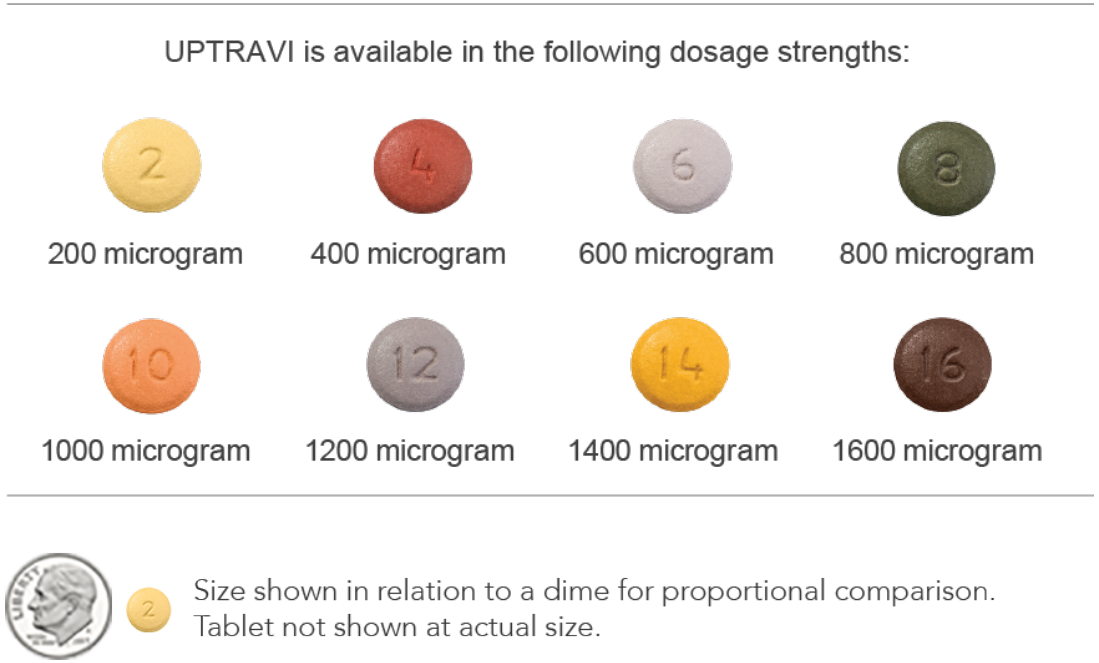
Tapson VF et al. Freedom-C2. *Chest* 2013; 144: 952-58.

Orenitram Conclusion

- Studies of short duration 12-16 weeks
- Monotherapy benefit compared to dual therapy lack thereof
- Limited time with diagnosis of PAH
- Slow titration required to limit ADEs
- Ideal place in therapy?
- Correct strengths to stock

Selexipag (Uptravi®)

- MOA: Selective prostacyclin IP receptor agonist.
- Dosing: (200 mcg-1600 mcg tablets): 200 mcg twice daily increasing weekly by 200 mcg twice daily based on patient tolerance. Max dose of 1600 mcg twice daily.
- PK: F= rapid/complete, D: PPB 99%; M/E: Hepatic (hepatic carboxylesterase, CYP 2C8 and 3A4), Elimination Bile, T ½= 10 hours
- ADRs: headache, diarrhea, jaw pain, nausea, flushing
- Pregnancy: No human data. Safety in animals documented.
- Drug Interactions: Gemfibrozil, 2C8 inhibitors



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LexiComp Uptravi Prescribing Information 2016

Selexipag GRIPHON

Patients: N = 1156 (50% WHO II and III), mean 6MWD 358m, 55% PAH, ERA 16%, PDE 33%, ERA + PDE 31%)

Design: Randomized, DB, MC 26 week trial

Study Dose: Selexipag 200 mcg twice daily ↑ 200 mcg weekly based on patient tolerance or max dose of 1600 mcg twice daily.

Primary Outcome: Composite death or complication due to PAH

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Sitbon O et al. *N Engl J Med* 2015; 373: 2522-33.

Selexipag GRIPHON Results…..

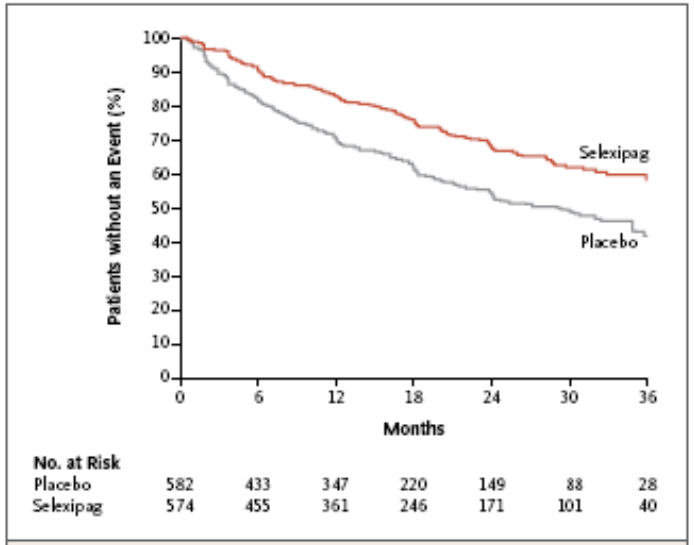

Figure 2. Primary Composite End Point.

Shown are Kaplan–Meier curves for the primary composite end point of death (from any cause) or a complication related to pulmonary arterial hypertension (disease progression or worsening of pulmonary arterial hypertension that resulted in hospitalization, initiation of parenteral prostanoid therapy or long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy) up to the end of the treatment period (defined for each patient as 7 days after the date of the last intake of selexipag or placebo) in the selexipag and placebo groups. A significant treatment effect in favor of selexipag versus placebo was observed (hazard ratio, 0.60; 99% CI, 0.46 to 0.78; P<0.001 with the use of a one-sided log-rank test). The analysis took into account all available data, whereas the Kaplan–Meier curve is truncated at 36 months.

Table 2. End Points Related to Pulmonary Arterial Hypertension and Death.*

End Point	Placebo (N=582)	Selexipag (N=574)	Hazard Ratio (99% or 95% CI)†	P Value‡
	no. of patients (%)			
Primary end point: composite of death or a complication related to PAH up to the end of the treatment period§				
All events	242 (41.6)	155 (27.0)	0.60 (0.46–0.78)	<0.001
Hospitalization for worsening of PAH	109 (18.7)	78 (13.6)		
Disease progression	100 (17.2)	38 (6.6)		
Death from any cause	18 (3.1)	28 (4.9)		
Initiation of parenteral prostanoid therapy or long-term oxygen therapy for worsening of PAH	13 (2.2)	10 (1.7)		
Need for lung transplantation or balloon atrial septostomy for worsening of PAH¶	2 (0.3)	1 (0.2)		
Secondary end point: death due to PAH or hospitalization for worsening of PAH up to the end of the treatment period§‖				
All events	137 (23.5)	102 (17.8)	0.70 (0.54–0.91)	0.003
Hospitalization for worsening of PAH	123 (21.1)	86 (15.0)		
Death due to PAH	14 (2.4)	16 (2.8)		
Secondary end point: death up to the end of the study‖**				
Death due to PAH	83 (14.3)	70 (12.2)	0.86 (0.63–1.18)	0.18
Death from any cause	105 (18.0)	100 (17.4)	0.97 (0.74–1.28)	0.42

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Sitbon O et al. *N Engl J Med* 2015; 373: 2522-33.

Endothelin Receptor Antagonists

ET1 → smooth muscle contraction and proliferation

ETA: vasoconstriction
ETB: vasoconstriction/vasodilation, ET1 clearance, liver toxicity?

Bosentan: ETA + ETB
Ambrisentan: ETA
Macitentan: ETA + ETB

University Hospitals

Steiner MK. Optimizing endothelin receptor antagonist use in the management of pulmonary arterial hypertension. *Vascular Health and Risk Management* 2008: 4: 943-952.

Bosentan (Tracleer)

- Dosing: (62.5 mg and 125 mg tablets) 62.5 mg bid for 4 weeks increasing to 125 mg bid for maintenance
- PK: F = 0.5, PPB: 98%, M/E: Hepatic CYP 2C9 and 3A4 three metabolites (one active), T ½ 5 hours (feces)
- ADRs: edema, headache, anemia, spermatogenesis inhibition (↓25%), hepatic transaminase elevation, respiratory tract infection
- Pregnancy X
- Drug Interactions: CYP 2C9, 3A4 (↓ PDE5, OC…)
- REMS: TAP (Tracleer Access Program): Pregnancy test BL and monthly with 2 forms of contraception (induced 3A4 OC interaction), LFT testing BL and monthly

62.5 mg and 125 mg tablets

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LexiComp Tracleer Prescribing Information 2014

Bosentan BREATHE-1

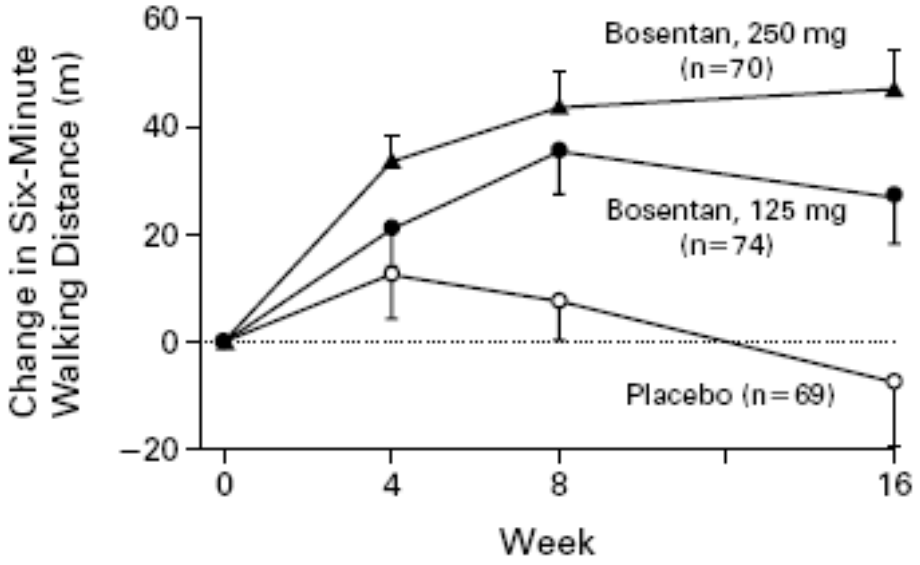

Figure 1. Mean (±SE) Change in Six-Minute Walking Distance from Base Line to Week 16 in the Placebo and Bosentan Groups.

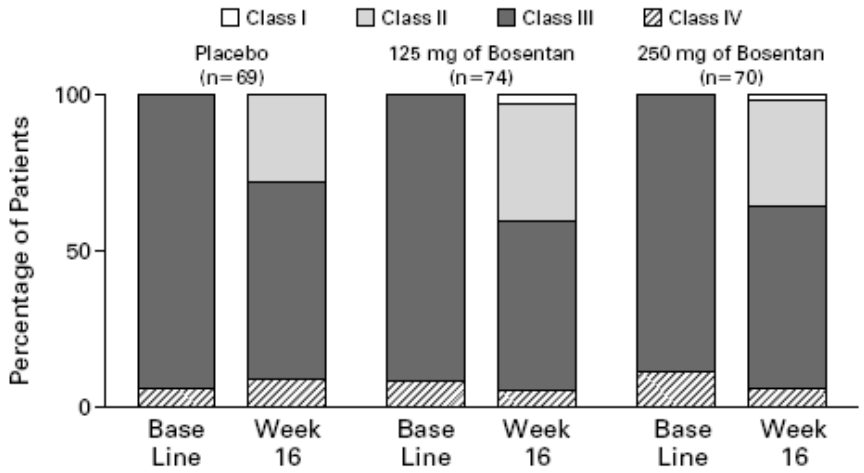

Figure 3. Change in World Health Organization Functional Class from Base Line to Week 16 in the Placebo and Bosentan Groups.
Higher classes indicate a greater severity of disease.

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Rubin LJ et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 346: 896-903.

Bosentan BREATHE-1 ADRs

TABLE 3. MOST FREQUENT ADVERSE EVENTS IN THE PLACEBO AND BOSENTAN GROUPS.*

EVENT	PLACEBO (N=69)	BOSENTAN GROUP COMBINED (N=144)	P VALUE†	125 mg OF BOSENTAN (N=74)	P VALUE†	250 mg OF BOSENTAN (N=70)	P VALUE†
	no. (%)			no. (%)		no. (%)	
Headache	13 (19)	30 (21)	0.86	14 (19)	1.00	16 (23)	0.68
Dizziness	13 (19)	16 (11)	0.14	9 (12)	0.35	7 (10)	0.15
Worsening of symptoms of pulmonary arterial hypertension	13 (19)	11 (8)	0.02	7 (9)	0.15	4 (6)	0.02
Cough	8 (12)	8 (6)	0.16	4 (5)	0.23	4 (6)	0.24
Dyspnea	7 (10)	7 (5)	0.15	2 (3)	0.09	5 (7)	0.56
Syncope	4 (6)	13 (9)	0.59	6 (8)	0.75	7 (10)	0.53
Flushing	3 (4)	13 (9)	0.28	7 (9)	0.33	6 (9)	0.49
Abnormal hepatic function	2 (3)	13 (9)	0.15	3 (4)	1.00	10 (14)	0.03

*The groups shown represent the intention-to-treat population. P values for the comparison with placebo were obtained by Fisher's exact test.

†P values are for the comparison with the placebo group.

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Rubin LJ et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 346: 896-903.

Ambrisentan (Letairis)

- Dosing: (5 mg and 10 mg tablets): 5 mg daily increasing after a month to 10 mg daily if tolerated
- PK: F= dose related, D: PPB 99%; M/E: Hepatic (CYP 3A4, 2C19, UGTs), Elimination T ½= 9 hours
- ADRs: edema, headache, anemia, spermatogenesis inhibition, respiratory tract infection
- Pregnancy X
- Drug Interactions: Cyclosporine
- REMS: Letairis REMS. Women only. Pregnancy test BL and monthly with 2 forms contraception.

5 mg and 10 mg tablets

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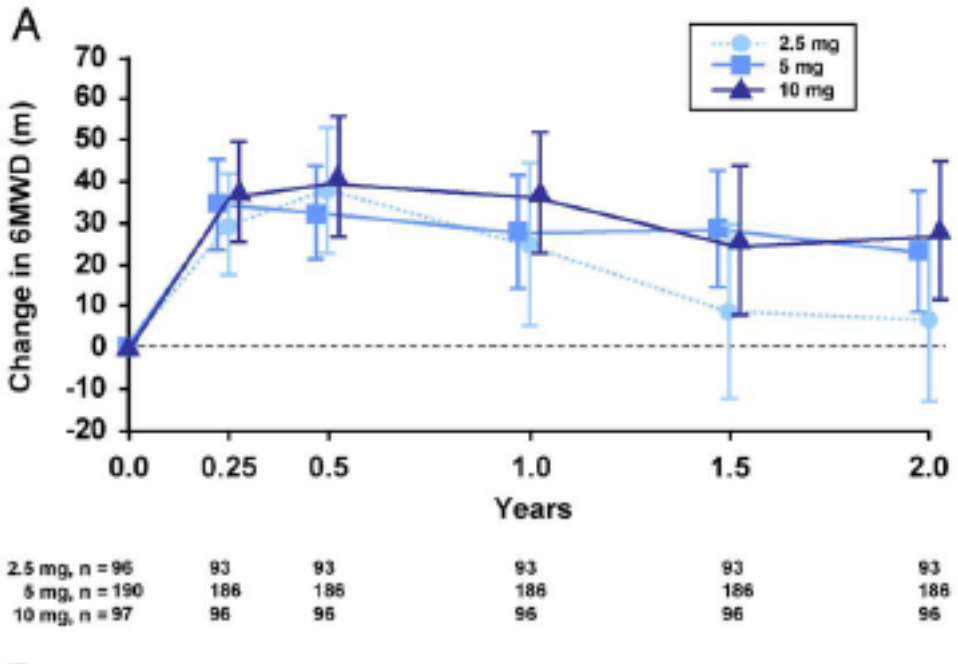
LexiComp Letaris Prescribing Information 2014

ARIES 1 and 2 Long Term Exension (Two Years)



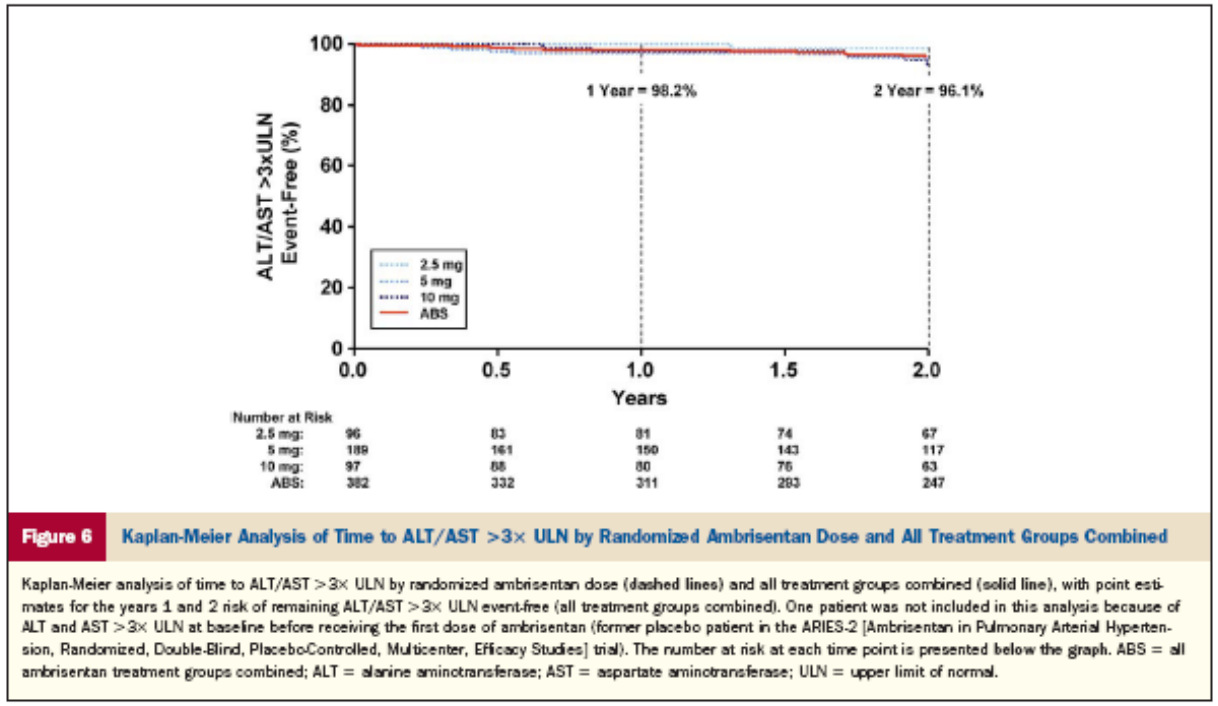


Figure 6 Kaplan-Meier Analysis of Time to ALT/AST >3× ULN by Randomized Ambrisentan Dose and All Treatment Groups Combined

Kaplan-Meier analysis of time to ALT/AST >3× ULN by randomized ambrisentan dose (dashed lines) and all treatment groups combined (solid line), with point estimates for the years 1 and 2 risk of remaining ALT/AST >3× ULN event-free (all treatment groups combined). One patient was not included in this analysis because of ALT and AST >3× ULN at baseline before receiving the first dose of ambrisentan (former placebo patient in the ARIES-2 [Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies] trial). The number at risk at each time point is presented below the graph. ABS = all ambrisentan treatment groups combined; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

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Ouidz Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 346: 896-903.

Patients that D/C Bosentan or Sitaxsentan D/T LFTs 3X Normal

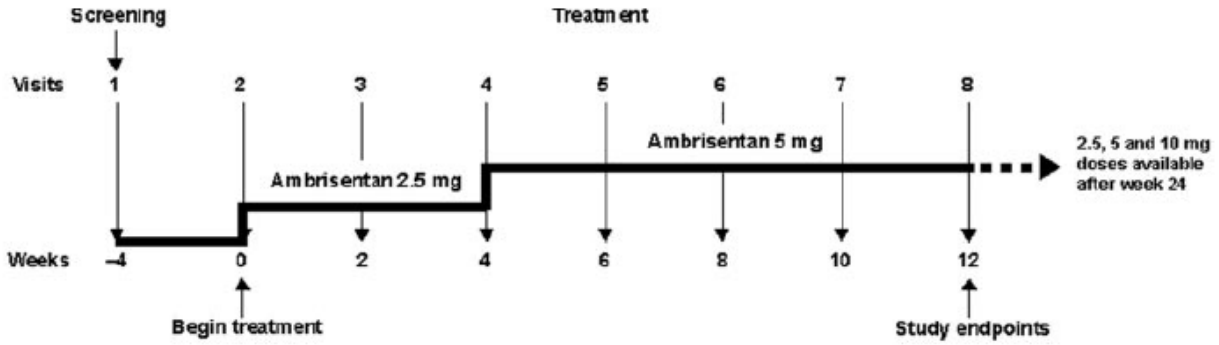


FIGURE 1. Study design.

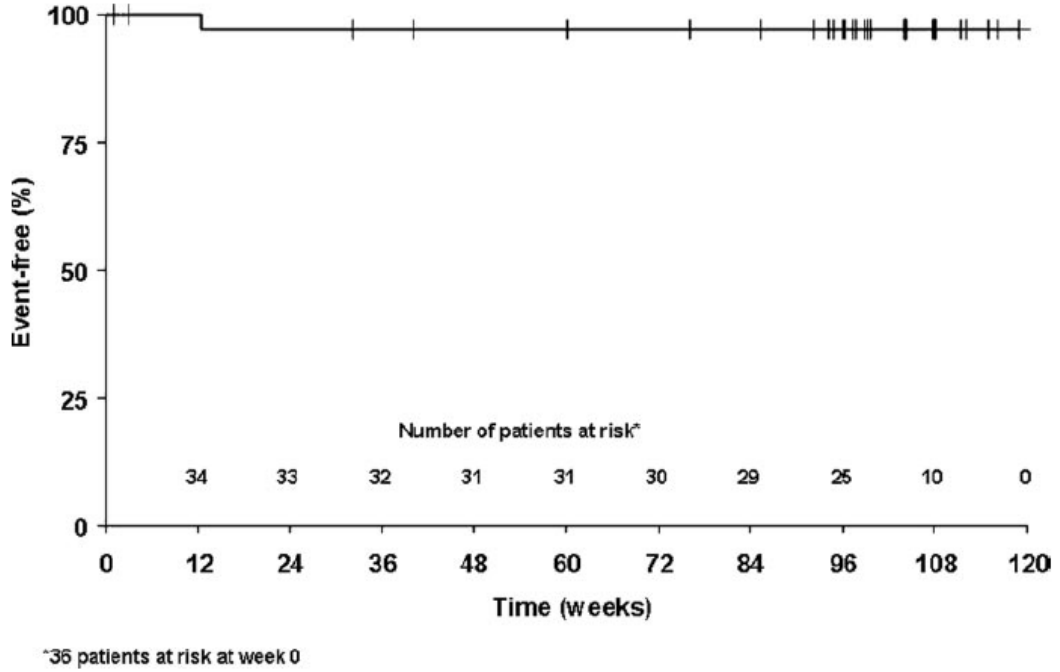


FIGURE 2. Kaplan-Meier curve of the time to first event. Time to first event is defined as ALT or AST concentrations more than three times ULN. The symbol (+) on the curve indicates the time at which subjects were censored.

University Hospitals

McGoon MD et al. Ambrisentan therapy in patients with PAH that discontinued bosentan or sitaxsentan due to liver function test abnormalities. *Chest* 2009; 135: 122-129.

Macitentan (Opsumit)

- Dosing: (10 mg tablet): 10 mg daily
- PK: F= dose related, D: PPB 99%; M/E: Hepatic (active metabolite) CYP 3A4; Elimination Urine/Feces T ½ = 16 hours (metabolite 48, 40% activity)
- ADRs: edema, headache, anemia, spermatogenesis inhibition?, respiratory tract infection
- Pregnancy X
- Drug Interactions: Ketoconazole, Rifampin
- REMS: Opsumit REMS. Women only. Pregnancy test BL and monthly with contraception.

10 mg tablet

University Hospitals

LexiComp Opsumit Prescribing Information 2014

Macitentan SERAPHIN Results….

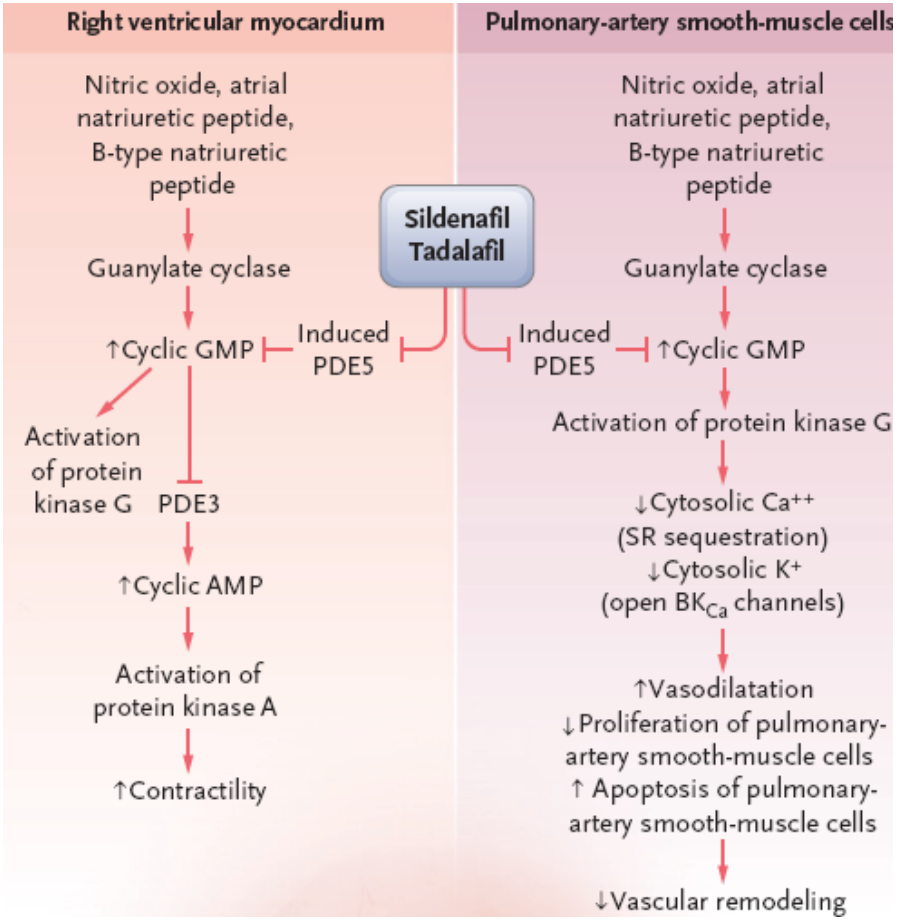
Table 2. Primary and Secondary End Points for Events Related to Pulmonary Arterial Hypertension and Death.*

End Point	Placebo (N=250)	Macitentan, 3 mg (N=250)	Macitentan, 10 mg (N=242)	Macitentan, 3 mg, vs. Placebo		Macitentan, 10 mg, vs. Placebo	
				Hazard Ratio (97.5% CI)	P Value	Hazard Ratio (97.5% CI)	P Value
	number of patients (percent)						
Event related to PAH or death as the first event							
All events	116 (46.4)	95 (38.0)	76 (31.4)	0.70 (0.52–0.96)	0.01	0.55 (0.32–0.76)	<0.001
Worsening of PAH	93 (37.2)	72 (28.8)	59 (24.4)				
Death from any cause†	17 (6.8)	21 (8.4)	16 (6.6)				
Prostanoid initiation	6 (2.4)	1 (0.4)	1 (0.4)				
Lung transplantation	0	1 (0.4)	0				
Death due to PAH or hospitalization for PAH as the first event							
All events	84 (33.6)	65 (26.0)	50 (20.7)	0.67 (0.46–0.97)	0.01	0.50 (0.34–0.75)	<0.001
Hospitalization for PAH	79 (31.6)	56 (22.4)	45 (18.6)				
Death due to PAH‡	5 (2.0)	9 (3.6)	5 (2.1)				
Death from any cause	19 (7.6)	21 (8.4)	14 (5.8)	0.97 (0.48–1.98)	0.92	0.64 (0.29–1.42)	0.20
Death due to PAH§	14 (5.6)	14 (5.6)	7 (2.9)	0.87 (0.37–2.04)	0.72	0.44 (0.16–1.25)	0.07
Death from any cause by the end of the study¶	44 (17.6)	47 (18.8)	35 (14.5)	1.05 (0.65–1.67)	0.83	0.77 (0.46–1.28)	0.25

University Hospitals

Pulido T et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013; 369: 809-18.

Phosphodiesterase 5 Inhibitors (PDE5)



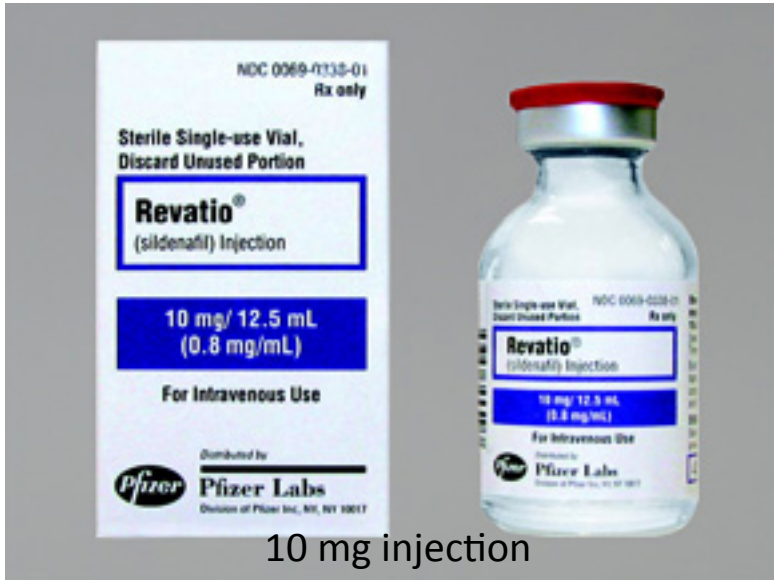
University Hospitals

Archer SL. Phosphodiesterase type 5 inhibitors for pulmonary hypertension. *N Engl J Med* 2009; 361: 1864-71.

Sildenafil (Revatio/Generic)

- Dosing (20 mg tablets): 20 mg po tid (maximum dose of 80 mg tid in clinical trials)
- Dosing (10 mg injection): 10 mg iv tid
- PK: A: 40% (onset 60 min), D: 96%PPB, Vd 105 L, M/E: Hepatic CYP 3A4 (major) and 2C9 (minor) active metabolite, T ½ 4 hours (feces 80%, urine 13%)
- Drug Interactions: nitrates, conivaptan, riociguat, etc…
- Pregnancy B
- ADRs: Flushing, headache, heartburn, muscle ache, epistaxis, hypotension, vision color changes/ blurred vision/photopsia (dose PDE6), NAION

20 mg tablet



10 mg injection

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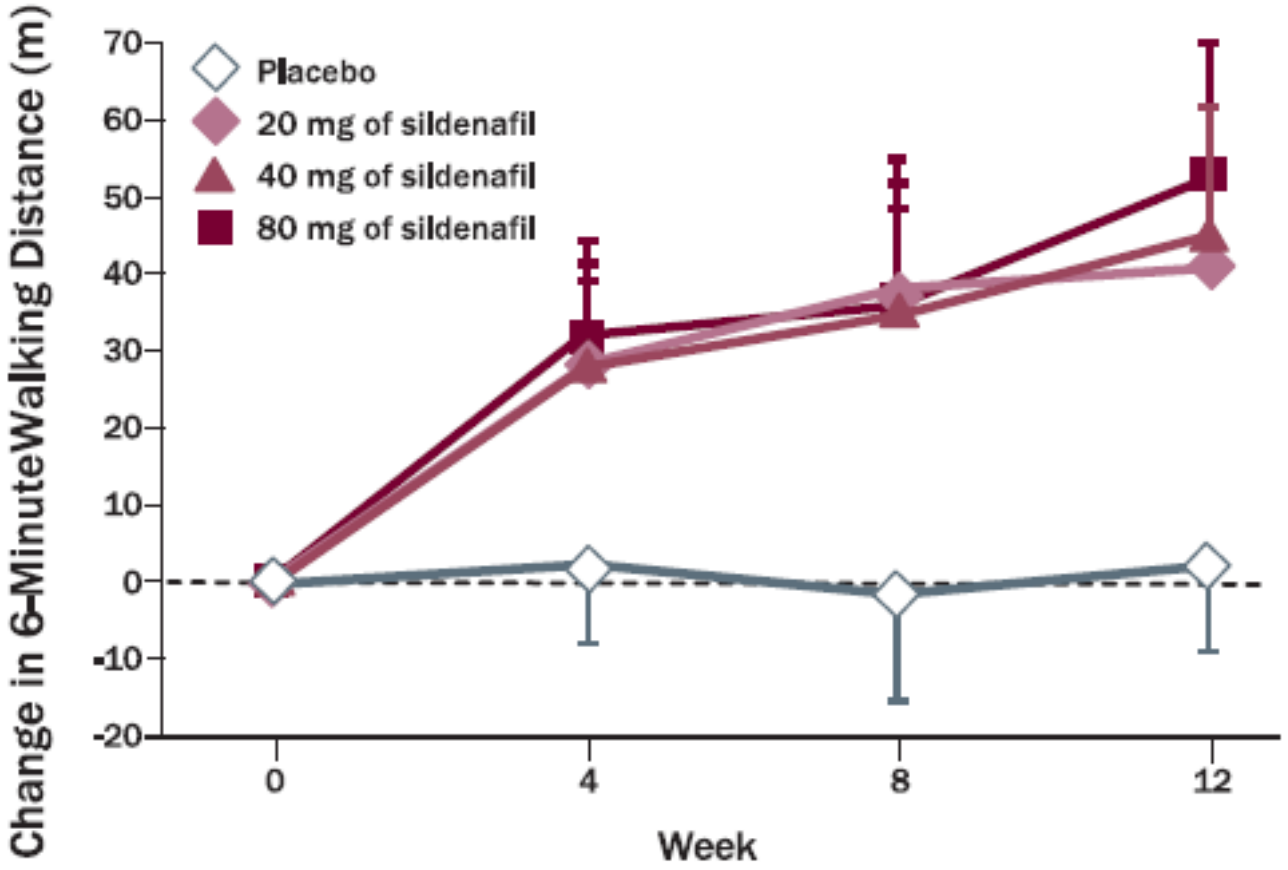
LexiComp Sildenafil Prescribing Information 2014

SUPER 1 and SUPER 2



- NS 6 min walk
- Dose related significant change hemodynamics
- NS clinical worsening
- Epistaxis (7% vs 1%)

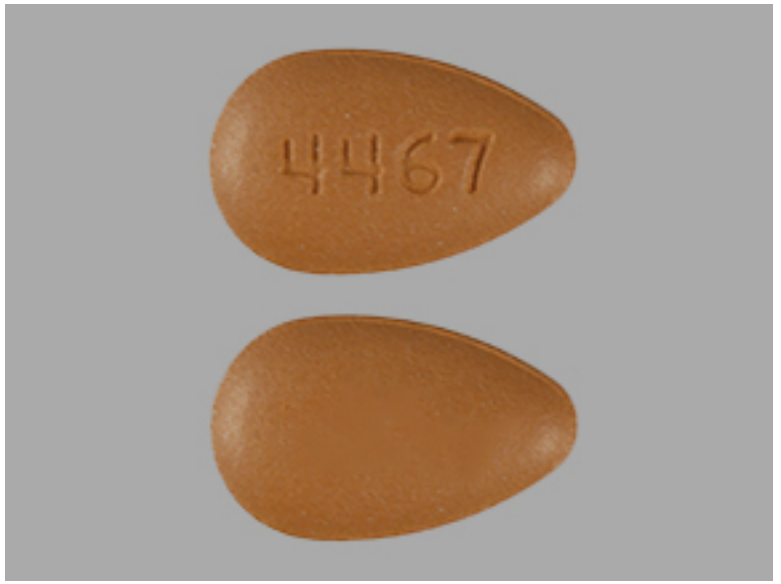
- SUPER 2 Extension 3 year study (80 mg): 60% improved or maintained functional status, 40% maintained or improved 6MWD, 79% survived

University Hospitals

Frumkin LR. The pharmacological treatment of pulmonary arterial hypertension. *Pharmacological Reviews* 2012; 64: 583-620.

Tadalafil (Adcirca)

- Dosing: (20 mg tablet): 40 mg once daily (↓ 50% renal impairment, 3A4 inhibitors, hepatic impairment), contraindicated in severe renal and/or hepatic disease
- PK: A: Not determined (Cmax 2 hours), D: PPB 94%, Vd 70L, M/E: Hepatic CYP 3A4 inactive metabolites, T ½ 16 hours (feces 60%, urine 36%)
- Drug Interactions: Nitrates, alpha blockers, CYP 3A4 inhibitors/inducers, riociguat
- Pregnancy B
- ADRs: Flushing, headache, heartburn, muscle ache, epistaxis, hypotension, vision color changes/blurred vision/photopsia (dose PDE6), NAION



Adcirca 20 mg tablet

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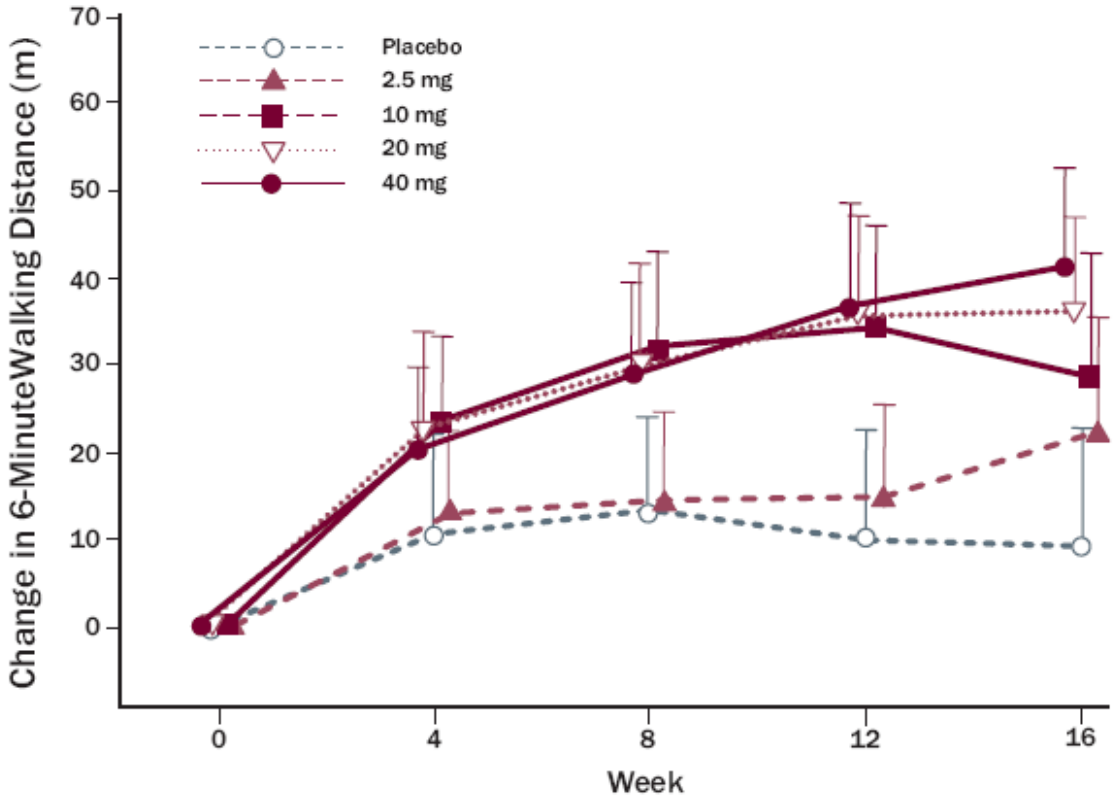
LexiComp Tadalafil Prescribing Information 2014

PHIRST

Tadalafil 16 week dose finding trial WHO II, III, 50% on bosentan background



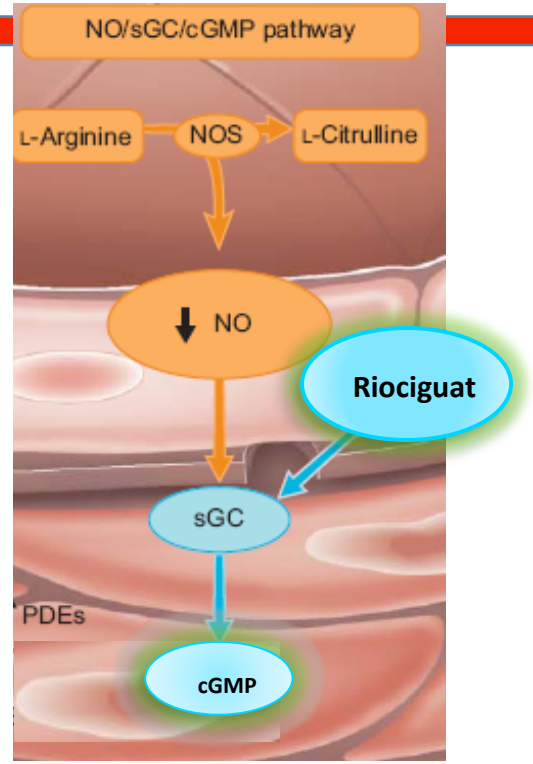
- All doses except 2.5 mg significant for 6MWD
- Significant hemodynamic changes at week 16 for 20 and 40 mg
- Bosentan + tadalafil combined NS
- Time to clinical worsening significant for 40 mg dose
- ADRs: headache, flushing, diarrhea

University Hospitals

Galie N et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009; 119: 2894-2903.

Riociguat (Adempas): Novel Mechanism of Action

- Soluble guanylate cyclase (sGC)
  - Nitric oxide (NO) receptor found in the cardiopulmonary system
  - NO + sGC → Increased generation of cyclic guanosine monophosphate (cGMP) → increased vasodilation
- Riociguat is an sGC stimulator with dual mode of action



1. Sensitizes sGC to NO by stabilizing NO-sGC binding
2. Directly stimulates sGC independent of NO

University Hospitals

Eur Resp J. 2009;33:785-92.

Eur Resp J. 2009;18:35-41.

Riociguat in: Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; Feb 28, 2014

Riociguat (Adempas)

- Indication: CTEPH WHO IV, PAH WHO I
- Dosing (0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg tablets): 1 mg tid (may reduce to 0.5 mg due to intolerance/hypotension). ↑ 0.5 mg tid every two weeks (SBP ≥ 95 mm Hg). Maximum dose 2.5 mg tid.
- PK: A: Complete (Cmax1.5 hours), D: PPB 95% Vd 30L, M/E: CYP 1A1 (active M1 metabolite inducible with smoking), 3A4, 3A5, 2C8, 2J2, T ½ 12 hours (feces 50%, urine 40%)
- Drug Interactions: PDE, nitrates, theophylline
- Pregnancy X
- Adempas REMS: Pregnancy test BL and monthly with 2 forms contraception. Only 30 days dispensed. Registration MD/Pharmacy.

0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg tablets

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LexiComp Adempas Prescribing Information 2014

Riociguat CHEST 1

- 16 week R, DB, PC, MC in N = 261 patients with CTEPH that is considered inoperable
- 6MWD 150-450 m, mPAP >25 mm Hg
- No concurrent therapy with PDE5, ERA, Prostenoid, Nitric Oxide
- 1:2 blocked randomization placebo: riociguat
- Riociguat 1 mg tid dosed based on SBP and tolerance to maximum of 2.5 mg tid to week 8 continued until week 16
- Primary Outcome: change in 6MWD
- Secondary Outcomes: hemodynamic, NT-proBNP, change in WHO functional class, clinical worsening, Borg dyspnea score, QOL scores, adverse effects

University Hospitals

Ghofrani H et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2013: 369: 319-329.

CHEST 1 Demographics

- 65% female
- Mean age 60 yo
- WHO II, III
- 6MWD 345 m

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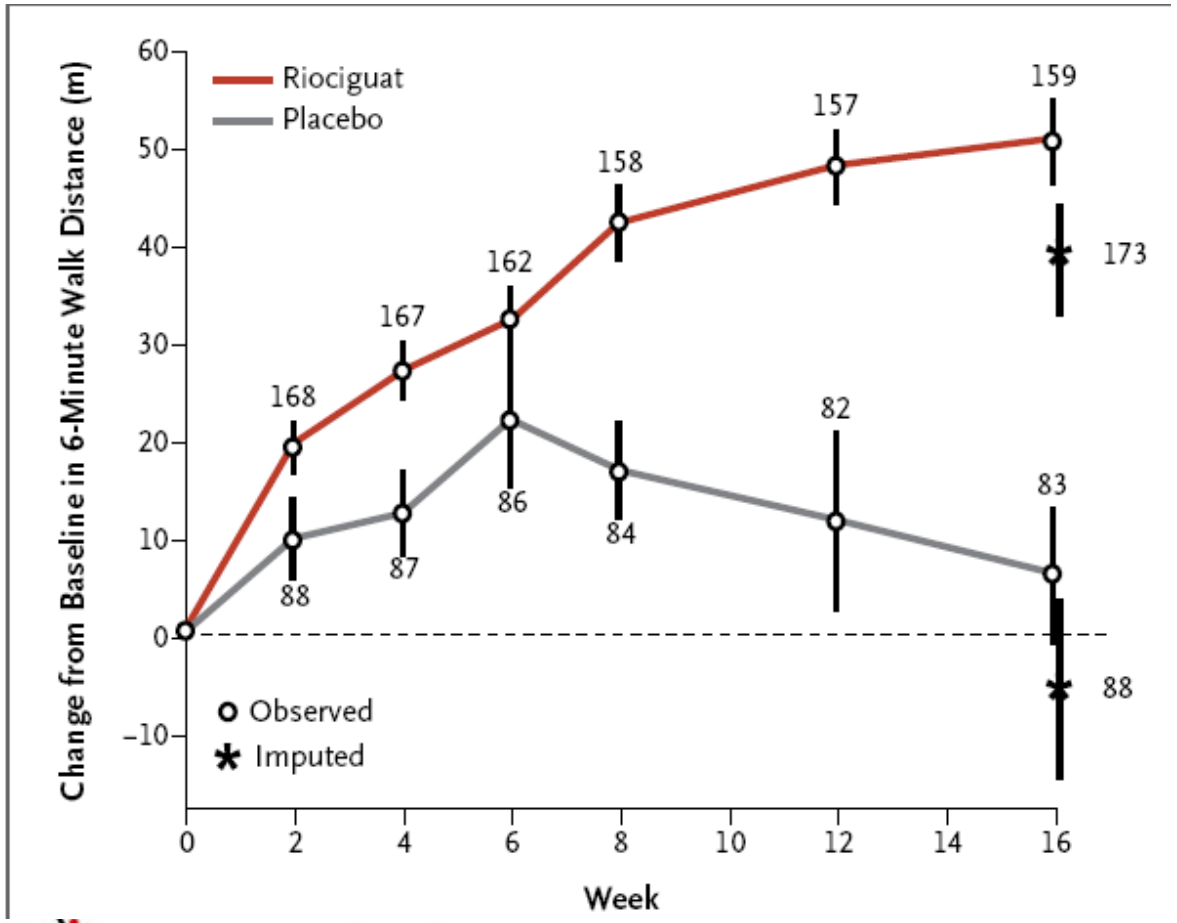
Ghofrani H et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2013: 369: 319-329.

CHEST 1 Results



- Mean change in PAP 5 mm Hg
- Mean change in MAP 9 mm Hg
- Mean change in CO 0.9 L/min
- 21% moved to lower WHO Class vs 14%
- NT-proBNP (pg/ml) -291 vs +76
- Borg dyspnea score -0.8 ± 2 vs +0.2 ± 2.4
- Clinical worsening 2% vs 6%

University Hospitals

Ghofrani H et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2013: 369: 319-329.

Adverse Events

Adverse Event	Riociguat PATENT-1 N=254 % (N)	Riociguat CHEST-1 N=173 % (N)	Pooled Placebo N=214 % (N)
Any	89 (227)	92 (159)	76 (162)
Headache	27 (69)	25 (43)	17 (37)
Dyspepsia	19 (48)	18 (31)	8 (17)
Peripheral edema	17 (44)	16 (27)	15 (32)
Diarrhea	14 (35)	10 (17)	8 (17)
Hypotension	10 (25)	9 (16)	3 (6)
Dizziness	16 (40)	23 (39)	12 (25)
Discontinued Study Drug due to Adverse Event	3 (8)	3 (5)	5 (11)

University Hospitals

N Engl J Med. 2013;369(4):319-29.
N Engl J Med. 2013;369(4):330-40.

Adempas Conclusion

- Studies of short duration 12-16 weeks
- Only agent studied for CTEPH
- Benefit with/without ERA
- Slow titration required to limit ADEs
- Ideal place in therapy?
- Correct strengths to stock

iNOMax Vs Inhaled Epoprostenol

Aeroneb® Solo

Superior nebulizer drug delivery

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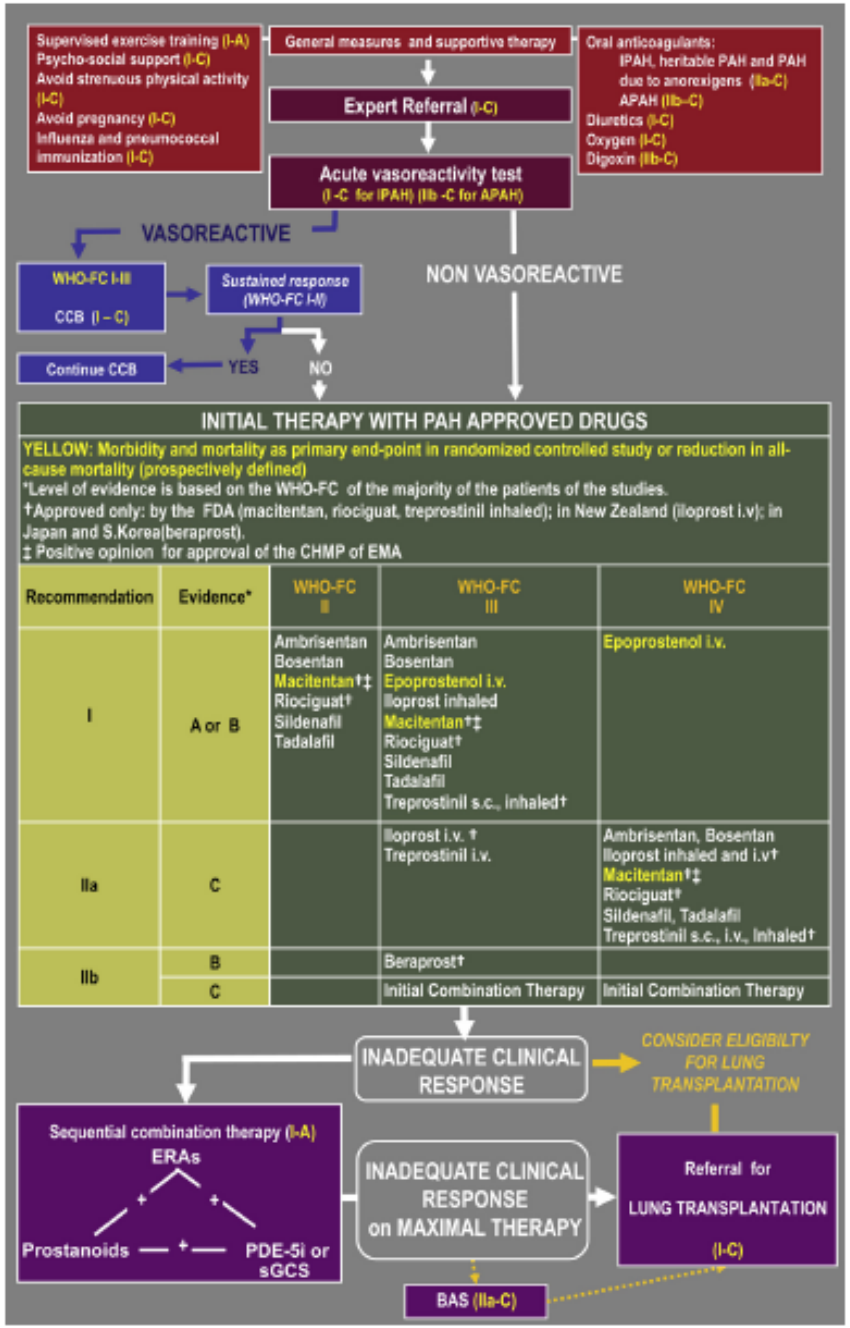

Figure 1 Evidence-Based Treatment Algorithm

Galie N. Updated treatment algorithm of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62: D60-72).

University Hospitals

Questions?

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