COVERAGE:

Drug therapy modalities for patients with demonstrated Pulmonary (Arterial) Hypertension (PH, PHTN, PAH), primary or secondary, are considered medically necessary. These modalities are:

- Conventional treatments, which include - calcium channel blockers, anticoagulants, oxygen, diuretics, and inotropics;
- Continuous intravenous administration of Epoprostenol sodium (Flolan) with a portable infusion pump attached to a permanent indwelling central venous catheter;
- Oral administration of Bosentan (Tracleer);
- Continuous subcutaneous administration of Treprostinil sodium (Remodulin) with a portable pager-sized microinfusion device; and
- Oral administration of Beraprost (orphan drug status).

The use of other pulmonary hypertension treatment modalities are considered experimental or investigational, including but not limited to:

- Aerosolized or inhaled forms of Prostacyclin (Ilioprost),
- Inhaled nitric oxide,
- Gene therapy.

The use of epoprostenol or endothelin antagonist drugs is considered experimental or investigational for other cardiovascular, pulmonary, or systemic applications, including but not limited to:

- Ischemic vascular diseases,
- Congestive heart failure,
- Chronic obstructive pulmonary disease (COPD), and
- Treatment of systemic peripheral vascular disease as associated with Scleroderma and other connective tissue disorders.

DESCRIPTION:

The human heart is responsible for two separate blood circulation systems; the right side sends blood to the lungs for oxygenation and the left side sends the oxygenated blood throughout the rest of the body. Pulmonary (arterial) hypertension (PH, PHTN, PAH) is a disease that affects the blood vessels in the lungs, specifically the pulmonary arteries. Sustained changes in these pulmonary arteries cause unusually high pressures that result in the heart being unable to pump against the pressure's resistance. This resistance over time will change the shape and size of the heart's right ventricle, ultimately leading to right ventricular failure and death. PH can be classified as either primary or secondary.
The increase in pulmonary arterial pressure (PAP) is often the result of another disease process known as secondary pulmonary hypertension (SPH, SPTHN). The underlying etiology may be:

- Connective tissue diseases (includes Scleroderma and its variants, as in the CREST syndrome – calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia),
- Congenital heart disease,
- Liver disease,
- Lung disease,
- Drug abuse (appetite suppressants included), or
- HIV infection.

SPH therapy focuses on treatment of the underlying disease, but may also include therapy of the hypertension.

Primary pulmonary hypertension (PPH, PPHTN) is an uncommon but highly lethal disease (which is a disease process of it's own) NOT caused by any other condition. It is estimated that only approximately 10% of our nation's population are diagnosed with PH. Of that 10%, SPH accounts for 90% while PPH accounts for the remaining 10%. The greatest number of reported cases of PPH have been young females between the ages of 21 and 40, however, men and women of all ages can develop the disease.

Early symptoms are vague and include fatigue, dyspnea, and lightheadedness. As the disease progresses, cyanosis, lower extremity edema, angina, syncope, and tachycardia are present. Usually the more severe the symptoms, the more advanced the disease.

Testing is done to exclude other physical reasons for the symptoms. These tests include:

- Echocardiogram,
- Cardiac catheterization,
- Pulmonary function tests,
- Lung scan (ventilation-perfusion or "VQ" scan),
- Computed Axial Tomography of chest,
- Hematological Tests,
- Sleep studies, and
- Magnetic Resonance Imaging of chest.

The diagnostic criteria used by the National Institutes of Health as part of their patient registry include the following:

- mean PAP of more than 30 mm Hg with exercise;
- mean PAP of more than 25 mm Hg at rest;
- exclusion of left-sided cardiovascular disease, myocardial disease,
congenital heart disease, or clinically important respiratory, connective tissue, or chronic thromboembolic diseases.

Once PH has been diagnosed, the disease is classified based upon the patient's toleration of daily living activities. This is called the "functional classification", which was developed by the New York Heart Association (NYHA). The classifications are:

- **Class I (1)** - Patients who have NO symptoms, such as tiredness, palpitations, shortness of breath, chest pain, etc.;
- **Class II (2)** - Patients who are comfortable when resting, but experience the above symptoms with basic ordinary physical activity;
- **Class III (3)** - Patients who are comfortable when resting, but experience the above symptoms with less-than-ordinary physical activities; and
- **Class IV (4)** - Patients who experience the above symptoms even at rest.

Since there is no cure for PH, treatment is done to relieve the symptoms. Conventional treatments include:

- Calcium channel blockers as vasodilators - used to lower pressure,
- Anticoagulants - used to reduce thrombosis,
- Oxygen - used to ease breathing,
- Diuretics - used to relieve the swelling in abdomen and lower extremities, and
- Inotropics - used to improve the force of contraction of the heart and slowing the heart rate.

Lung (single or double) transplantation and combined heart-lung transplantation have been performed in patients refractory to medical management.

The U.S. Food and Drug Administration (FDA) have approved newer drug treatments (which mimic the body's natural prostaglandins). These treatments:

- decrease pulmonary vascular resistance by dilating the pulmonary blood vessels and various blood vessels throughout the body and
- increase cardiac output by improving heart activity.

**EPROPROSTENOL SODIUM (FLOLAN)**

Epoprostenol sodium (also referred to as prostacyclin, PGI₂, PGX) is a naturally occurring prostaglandin. PGX has an extremely short half-life (approximately 6 minutes or less) and thus is administered intravenously with a portable infusion pump attached to a permanent indwelling central venous catheter. In 1995, the FDA approved Flolan (brand name for Epoprostenol sodium) for treatment of patients with PH and NYHA Class III or IV symptoms, where it may be used as a bridge to
lungs and consequently may not be candidates for lung transplant. However, some patients with good responses have been able to defer transplantation. In 2000, there was an additional FDA approval for the treatment of PH "associated with the scleroderma spectrum of diseases (PH/SSC) in NYHA classes III and IV patients who do not respond adequately to conventional therapy." There is no set dose for Flolan; the dose that is given is based on the amount of relief it provides the patient (of the PH symptoms) and the patient's ability to handle the medication side effects. Continuous intravenous infusion treatment with Flolan requires these three steps:

- Initial dose-ranging study, which is typically performed as an inpatient. The pulmonary capillary wedge pressure is monitored and the infusion rate of the drug is increased until dose-limiting pharmacologic effects such as nausea, vomiting, or headaches are elicited. Some practitioners may consider the initial dose-ranging study optional.
- Insertion of a central venous catheter and attachment to a portable infusion pump. Since rebound PH may recur if the drug is abruptly withdrawn, the drug labeling advises that all patients should have access to a backup infusion pump and intravenous infusion set.
- Ongoing maintenance of the portable infusion pump and treatment of complications related to the pump. Complications include catheter thrombosis, sepsis, and pump malfunction. In the clinical trials, a cold pouch and frozen gel packs were used to facilitate extended use at ambient temperatures.

**BOSENTAN (TRACLEER)**

Bosentan is an oral form of PGX. It blocks the action of a hormone called endothelin (found in higher levels of patients with PPH and SPH). This hormone is produced by the lung and is damaging to the lung and pulmonary arteries. Bosentan is an "antagonist" drug, which lowers the amount of endothelin and reverses its effects. In 2001, the FDA approved Tracleer (brand name for Bosentan) for treatment of patients with PH and World Health Organization (WHO) Class III or IV symptoms. It is to improve exercise ability and decrease the rate of disease progression. Oral administration of Bosentan includes incremental increases of dosage amounts to achieve a maintenance level.

**TREPROSTINIL SODIUM (REMODULIN)**

Treprostinil sodium (UT-15, Uniprost) is a synthetic form of prostacyclin. It has a longer dilation action of 4 to 6 hours versus the short half-life of Flolan. Because of the long acting properties, UT-15 can be delivered under the skin (subcutaneously) rather than directly into the bloodstream. In 2002, the FDA approved Remodulin (brand name for Treprostinil sodium) for the subcutaneous treatment of patients with PH and NYHA Class II or IV symptoms to diminish symptoms associated with exercise.
BERAPROST

Beraprost is a chemically stable form of prostacyclin. It dilates blood vessels, prevents platelet aggregation (clot formation), and also prevents an increase of smooth muscle cells surrounding the blood vessels. The FDA has listed Beraprost with an Orphan designation for the proposed of treating patients with PH and any NYHA classification.

Orphan designation by the FDA was devised to provide financial incentives to drug manufacturers for the research and development of drugs with a small target treatment population (less than 200,000); it does not constitute final FDA approval. Ongoing clinical trials will be required to prove whether Beraprost will be safe and effective for the treatment of peripheral vascular disease (PVD).

ILIOPROST

Ilioprost is an aerosolized or inhaled form of PGX. Ilioprost selectively dilates the pulmonary vessels by depositing itself in the lung's alveoli during normal breathing activity. As a result, Ilioprost reduces and relieves pulmonary vascular resistance. Patients inhale 6 to 8 puffs every 2 to 3 hours. This therapy is mainly utilized in Europe. Clinical studies are being planned in the United States.

INHALED NITRIC OXIDE

Inhaled nitric oxide (NO), is a potent pulmonary vasodilator that is inhaled and delivered like supplemental oxygen. Researchers note that it can reduce pulmonary artery pressure in some patients with PPH. Its use is being studied alone and in conjunction with other medications.

GENE THERAPY

Ongoing research into gene therapy may someday offer a cure to PH once the exact genetic defect is identified.

RATIONALE:

EPOPROSTENOL SODIUM (FLOLAN)

The original FDA approval of Epoprostenol was based on a 12-week trial of 81 patients with NYHA Association Class III or Class IV primary pulmonary hypertension who were randomized to receive either Epoprostenol or conventional medical management. Compared to conventional therapy, the continuous intravenous infusion of Epoprostenol produced symptomatic and hemodynamic improvement, as well as improved survival in patients with severe primary pulmonary hypertension. The long-term effects of Epoprostenol infusion,
specifically whether patients remain sensitive to the drug over prolonged periods of time, has not been as thoroughly studied. However results of smaller uncontrolled case series suggest that with increasing dosages the beneficial effect is maintained up to 18 months and that mortality is decreased compared to historical controls. In 1998 McLaughlin and colleagues reported on a case series of 27 patients treated with epoprostenol who were followed for a mean of 16 months. All patients had improvement in symptoms such as NYHA classification and exercise duration. While pulmonary vascular resistance declined only 23% acutely, in response to a test dose of adenosine (another vasodilator), over long-term follow-up the vascular resistance fell by 53%. These results suggest that the beneficial effects of Epoprostenol are not solely related to vasodilation, but perhaps related to anticoagulant and endothelial cytoprotective effects. In 2000, Flolan received an additional FDA approval as a treatment of pulmonary hypertension associated with scleroderma.

**BOSENTAN (TRACLEER)**

The FDA with the help of the Cardiovascular and Renal Drugs Advisory Committee determined that Tracleer is an effective treatment based on the results of two randomized, placebo-controlled clinical trials involving a total of 245 patients. In both studies, compared to the placebo, Tracleer or the placebo, were given in addition to any other medications currently prescribed. In both studies, treatment with Tracleer resulted in a significant improvement, in the six minute walking distance of patients receiving Tracleer (an additional 35 meters in one study and 54 meters in another). The improvement in walking distance was apparent after one month and fully developed by about two months of treatment. Significant improvement was maintained for up to seven months of Tracleer treatment.

**TREPROMSTINIL SODIUM (REMODULIN)**

Again in 2000, Remodulin was granted a priority review. In 2002, the FDA and the Cardiovascular and Renal Drugs Advisory Committee approved Remodulin despite a recommendation by FDA reviewers for non-approval. The priority review and approval was based on two placebo-controlled, 12 week studies enrolling a total of 470 patients with PAH and administering Remodulin by continuous subcutaneous infusion. The mean distance walked at baseline was 327 meters in six minutes for both the Remodulin and placebo groups. At 12 weeks of therapy, the mean distance decreased by two meters for the Remodulin group and 21 meters for the placebo group. So the mean distance walked in both groups decreased despite the therapy and the primary endpoint for these trials was not met until data from these two studies were combined.

**BERAPROST**

Beraprost was given orphan drug status in 1999. Ongoing clinical trials will be required to prove whether Beraprost will be safe and
effective for the treatment of peripheral vascular disease (PVD). According to the manufacturing company, Beraprost was proven to be safe and effective for the treatment of PVD in clinical studies conducted outside the US and has been approved for treatment of PVD in Japan since 1994.

**ILIOPROST**

Ilioprost is mainly utilized in Europe. Clinical studies are being planned in the United States. There is no available scientific literature published in peer-reviewed journals. The available literature is inadequate to evaluate the effectiveness of Ilioprost therapy for PH treatment.

**INHALED NITRIC OXIDE AND GENE THERAPY**

There is no available scientific literature published in peer-reviewed journals. There is a lack of literature to adequately evaluate the effectiveness of these types of therapies to reduce symptoms of or eventually eliminate PH.

**PRICING:**

None

**REFERENCES:**

PULMONARY (ARTERIAL) HYPERTENSION (PH, PHTN, PAH) DRUG THERAPIES
RX501.056
POSTED DATE: 6/11/2003
EFFECTIVE DATE: 8/15/2003

(Website 12/6/2002)

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DISCLAIMER:

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