Pulmonary arterial hypertension (PAH) is a deadly disease that affects between 10,000 and 20,000 people in the U.S. — most of them women. PAH is a progressive condition and without treatment, only about 70 percent of patients survive a year after diagnosis, with only about one-third making it to five years.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\) It is also an extremely expensive condition to treat. In 2016, America’s Health Insurance Plans, an industry organization of health insurers, estimated that average drug spending for patients with PAH ranged from $103,464 to $196,660 a year.\(^4\) Two of the five most expensive drugs covered by Medicare were PAH treatments: Remodulin (injectable treprostinil) at $144,070 per patient per year and Tyvaso (inhaled treprostinil) at $107,489, according to another report.\(^5\)

Most existing PAH drugs provide symptomatic relief; they make patients more comfortable and enable a somewhat greater level of physical activity.\(^6\) A few slow the progression of the disease. Treatment for PAH improved radically in 2013, when three key drugs (Orenitram, Adempas, and Opsumit) were granted approval and again in 2015 when Uptravi was approved by the U.S. Food and Drug Administration (FDA).\(^7\)\(^,\)\(^8\) Adempas (riociguat) introduced the first novel mechanism of action for the treatment of PAH in a decade, while Opsumit (macitentan) expanded the number of agents in the same mechanistic class as Tracleer (bosentan). As the first oral prostacyclin PAH treatments, Orenitram (oral treprostinil) and Uptravi (selexipag) altered PAH treatment significantly as well – until then, all prostacyclin PAH medications had to be administered by injection or inhalation. Today, the PAH marketplace faces a turning point of another sort, as several important drugs are on the verge of coming off patent and facing generic competition. Simultaneously, pharmaceutical companies are continuing to explore both new mechanisms of action and new formulations of existing drugs to better treat PAH.

### Some of the Current PAH Treatments

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Route</th>
<th>Approval Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracleer</td>
<td>bosentan</td>
<td>oral</td>
<td>Nov. 2001</td>
</tr>
<tr>
<td>Remodulin</td>
<td>treprostinil</td>
<td>subcutaneous infusion</td>
<td>May 2002</td>
</tr>
<tr>
<td>Letairis</td>
<td>ambrisentan</td>
<td>oral</td>
<td>June 2007</td>
</tr>
<tr>
<td>Adempas</td>
<td>riociguat</td>
<td>oral</td>
<td>Oct. 2013</td>
</tr>
<tr>
<td>Opsumit</td>
<td>macitentan</td>
<td>oral</td>
<td>Oct. 2013</td>
</tr>
<tr>
<td>Orenitram</td>
<td>treprostinil</td>
<td>oral</td>
<td>Dec. 2013</td>
</tr>
<tr>
<td>Uptravi</td>
<td>selexipag</td>
<td>oral</td>
<td>Dec. 2015</td>
</tr>
</tbody>
</table>

### Wearing out the Heart

PAH is one of five forms of pulmonary hypertension. Most are caused by a variety of heart, vascular, and lung diseases.\(^9\) PAH, on the other hand, is caused by constriction and thickening of the arteries in the lungs, which makes it more difficult for the heart to pump blood through them. It can be caused by toxins, the use of certain drugs (most notably the weight-loss drug fenfluramine — which was withdrawn from the market 20 years ago), or as a result of other conditions, such as congenital heart disease, HIV infection, and sickle cell disease.\(^10\) In some cases — such as idiopathic PAH — the causes may remain unknown, or the condition could be the result of inherited genetic mutations.\(^11\)
PAH overburdens the heart and makes it difficult for the lungs to adequately oxygenate the blood. As a result, patients experience chest pain and shortness of breath. As the disease progresses, they may be exhausted by even modest physical activity. In late-stage PAH the right side of the heart, which pumps blood through the lungs, becomes worn out and fails. When that happens, the patient requires surgery to survive: a transplant to replace the lungs (or sometimes both heart and lungs) or a procedure to reconfigure the circulation. Unfortunately, in many cases, the patient dies.

**PAH is not curable and there is no reliable way to reverse damage to the pulmonary blood vessels.**

Most therapies for the disease focus on various strategies for vasodilation — widening the arteries to promote better blood flow — and prevention of additional arterial wall thickening.

### An Explosion of Generics (maybe)

Generics of PAH drugs — notably Pfizer's Revatio (sildenafil), and GlaxoSmithKline's Flolan (epoprostenol) — have offered payors additional formulary and utilization management options in the last few years. And a wave of new generics over the next few years could help provide additional cost-control options. There are several hurdles to a mass entry of generics, including litigation over patent expirations and risk evaluation and mitigation strategy (REMS) programs for several drugs. REMS programs aim to ensure the drugs being prescribed are used safely, but can also prevent potential generic manufacturers from obtaining samples, thereby impeding their ability to introduce generic competition. Potential generics in the PAH pipeline include:

#### Treprostinil

All of the drugs based on treprostinil could potentially see generic competition over the next few years, as a result of patent challenges filed against manufacturer United Therapeutics (UTC).

- The company has already settled lawsuits by agreeing to let several generic drug manufacturers introduce generic versions of Remodulin, the injectable form of the drug. Generic manufacturer Sandoz is expected to be first to market, with an anticipated launch in the second quarter of this year. Other manufacturers — Teva, Par, and Dr. Reddy’s — are expected to follow by the end of the year.
- Generic drug manufacturers Watson and Actavis have launched challenges to Tyvaso (the inhaled form) and Orenitram (the oral form).
- An action brought by the manufacturer SteadyMed recently overturned a key patent covering all three drugs. UTC is appealing the decision and maintains that other valid patents still cover the products. Remodulin and Tyvaso are an inhaled and infused drug respectively, and therefore the most expensive PAH drugs currently on market. Generic competition could significantly reduce their cost for payors and patients.

#### Ambrisentan

Letairis (ambrisentan), a member of the same drug class as Tracleer, may lose patent and exclusivity protection later in 2018, though it is unclear how quickly a generic will follow. A generic for Letairis could be significant because the drug, in combination with tadalafil (better known as the active ingredient in Adcirca), was the first combination therapy for PAH approved by the FDA. The two drugs taken together were shown to reduce worsening of the disease by nearly 50 percent compared to either separately. Generic tadalafil, meanwhile, is currently expected to launch in the second quarter of 2018.

#### Bosentan

Tracleer (bosentan), an oral drug that blocks the action of endothelin, a natural substance that causes blood vessels to constrict, went off patent in 2015 yet still has no generic competitor. Tracleer is one of the drugs requiring a REM strategy, which could pose a challenge for potential generic manufacturers.
Looking for a Disease Changer

Much of the research on PAH drugs in recent years has been to explore combination therapies, which has yielded promising results, especially for the ambrisentan-tadalafil combination. There is ongoing research on new formulations and drug delivery systems, especially for treprostinil, which has an extremely short half-life and is difficult for patients to tolerate by injection, although it may be years before any are approved or come to market. Candidates include a prefilled infusion pump, skin patches, and new inhalation devices, including ones that deliver a dry powder form of the drug.

In addition, bardoxolone, a drug developed by Reata Pharmaceuticals with a novel mechanism of action affecting gene expression, is in Phase III clinical trials with results expected late this year.

Perhaps most interesting of all is a partnership between Roche and the U.K. National Institute for Health Research Rare Diseases Translational Research Collaboration in which Actemra (tocilizumab), an immune suppressor used to treat rheumatoid arthritis, is being studied to see if it could help reverse PAH-induced damage to blood vessels. If it succeeds, it could become the first true disease-altering drug for the condition.

Insights offers context and perspective about key pharmacy and health care topics.

It has been a little more than 20 years since the FDA approved Flolan (epoprostenol), the first drug specifically intended for the treatment of PAH. In the intervening years, a dozen additional PAH treatments have come to market — an extraordinary number, given the extremely small patient population. Survival rates have roughly doubled. And yet PAH remains debilitating, progressive, and often fatal. More drugs are on the way, including several that may launch as early as next year. But a true disease-modifying treatment is at least a few years away, maybe more. In the meantime, accurate diagnosis, effective prescribing, and patient education and engagement remain the best tools for easing the immense burden of this rare disease.

Want to learn more about the PAH pipeline and the cost impact to your plan? Ask Us

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