United Therapeutics Announces FDA Approval Of The Implantable System For Remodulin®

July 31, 2018

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., July 31, 2018 /PRNewswire/ -- United Therapeutics Corporation (NASDAQ: UTHR) today announced approval by the U.S. Food and Drug Administration (FDA) of a New Drug Application (NDA) for the use of Remodulin (treprostinil) Injection in the Implantable System for Remodulin® (ISR).

The ISR has been developed under a collaboration with Medtronic (NYSE: MDT). In December 2017, Medtronic received FDA approval of a premarket application (PMA) for a proprietary intravascular infusion catheter to be used with its SynchroMed™ II implantable infusion pump and related infusion system components (together referred to as the Implantable System for Remodulin) in order to deliver Remodulin for the treatment of pulmonary arterial hypertension (PAH).

"We are extremely excited to offer this new option to patients suffering from PAH," said Martine Rothblatt, Ph.D., Chairman and Chief Executive Officer of United Therapeutics. "During the course of the *DelIVery* study, we received considerable physician and patient interest in the ISR. We are grateful to our collaborators at Medtronic for reaching this milestone and look forward to continuing our collaboration."

Remodulin was originally approved by the FDA to treat PAH by continuous subcutaneous and intravenous routes of administration in 2002 and 2004, respectively, using external pumps. In the case of intravenous users, the therapy can be very burdensome and brings a risk of sepsis due to the use of a central indwelling catheter.

The ISR provides patients a new option for delivery of intravenous Remodulin, where the entire delivery system is implanted into the body and will be refilled by healthcare professionals at intervals of up to 16 weeks depending on the patient's dose, using a syringe needle through the patient's skin.

"External infusion pumps have been used to deliver prostacyclins for PAH, but managing the therapy places a significant burden on patients, interferes with their daily activities, and runs a high risk of infections," said David Steinhaus, M.D., general manager of the Heart Failure business, part of the Cardiac and Vascular Group at Medtronic. "This fully implantable drug delivery system was designed to address these serious patient care concerns."

United Therapeutics funded and Medtronic conducted the *DelIVery for PAH* clinical trial, which was a safety study of a new implantable catheter designed for intravascular drug (Remodulin) delivery with the SynchroMed™ II implantable infusion pump. In 2013, the study met its primary objective of demonstrating a rate of catheter-related complications below 2.5 per 1,000 patient-days while using the fully implantable system ($p < 0.0001$).

About Remodulin (treprostinil) Injection

Indication

Remodulin is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%).

In patients with PAH requiring transition from epoprostenol, Remodulin is indicated to diminish the rate of clinical deterioration. Consider the risks and benefits of each drug prior to transition.

Important Safety Information for Remodulin

Warnings and Precautions

- Chronic intravenous (IV) infusions of Remodulin delivered with an external infusion pump using an indwelling central venous catheter are associated with the risk of blood stream infections (BSI) and sepsis, which may be fatal. Therefore, continuous subcutaneous (SC) infusion is the preferred mode of administration.
- Avoid abrupt withdrawal or sudden large reductions in dosage of Remodulin, which may result in worsening of PAH symptoms.
- Titrate slowly in patients with hepatic or renal insufficiency because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function.
- Remodulin is a potent pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with Remodulin may produce symptomatic hypotension
- Remodulin inhibits platelet aggregation and increases the risk of bleeding.

Adverse Reactions

- Adverse Reactions: In clinical studies of SC Remodulin infusion, the most common adverse events reported were infusion site pain and infusion site reaction (redness and swelling). These symptoms were often severe and sometimes required treatment with narcotics or discontinuation of Remodulin. The IV infusion of Remodulin with an external infusion pump has

been associated with a risk of blood stream infections, arm swelling, paresthesias, hematoma, and pain. Other common adverse events (≥3% more than placebo) seen with either SC or IV Remodulin were headache (27% vs. 23%), diarrhea (25% vs. 16%), nausea (22% vs. 18%), jaw pain (13% vs. 5%), vasodilatation (11% vs. 5%), edema (9% vs. 3%), and hypotension (4% vs. 2%).

Drug Interactions

- Remodulin dosage adjustment may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn.

Specific Populations

- In patients with mild or moderate hepatic insufficiency, decrease the initial dose of Remodulin to 0.625 ng/kg/min ideal body weight. Remodulin has not been studied in patients with severe hepatic insufficiency.
- Safety and effectiveness of Remodulin in pediatric patients have not been established.
- It is unknown if geriatric patients respond differently than younger patients. Caution should be used when selecting a dose for geriatric patients.
- There are no adequate and well-controlled studies with Remodulin in pregnant women. It is not known whether treprostinil is excreted in human milk.

Please see accompanying Full Prescribing Information for Remodulin.

For additional information, visit http://www.remodulin.com **or call the Customer Service Line at 1-877-UNITHER (1-877-864-8437).**

About United Therapeutics

United Therapeutics Corporation is a biotechnology company focused on the development and commercialization of innovative products to address the unmet medical needs of patients with chronic and life-threatening conditions. [uthr-g]

About Medtronic

Medtronic plc (www.medtronic.com), headquartered in Dublin, Ireland, is among the world's largest medical technology, services and solutions companies – alleviating pain, restoring health and extending life for millions of people around the world. Medtronic employs more than 86,000 people worldwide, serving physicians, hospitals and patients in more than 150 countries. The company is focused on collaborating with stakeholders around the world to take healthcare Further, Together.

Forward-looking Statements

Statements included in this press release that are not historical in nature are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include, among others, statements regarding the use of Implantable System for Remodulin. These forward-looking statements are subject to certain risks and uncertainties, such as those described in our periodic and other reports filed with the Securities and Exchange Commission that could cause actual results to differ materially from anticipated results. Such forward-looking statements are qualified by the cautionary statements, cautionary language and risk factors set forth in our periodic reports and documents filed with the Securities and Exchange Commission, including our most recent Annual Report on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K. We claim the protection of the safe harbor contained in the Private Securities Litigation Reform Act of 1995 for forward-looking statements. We are providing this information as of July 31, 2018, and assume no obligation to update or revise the information contained in this press release whether as a result of new information, future events or any other reason.

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