Implantable System for Remodulin® Brief Statement

Indications

The Implantable System for Remodulin is indicated for adult patients with Class I, II and III pulmonary arterial hypertension (PAH) receiving intravenous delivery of Remodulin.

Physicians prescribing this system for use with Remodulin must be familiar with the indications, contraindications, warnings, precautions, adverse events, and dosage and administration information described in the Remodulin drug labeling. The Model 201106 Refill Kit is intended for use in refilling the Medtronic SynchroMed II for ISR programmable infusion pump.

Contraindications

Contraindications for the Implantable System for Remodulin are listed by category.

System implantation – Implantation of the system is contraindicated:

- for NYHA Class IV PAH patients
- in the presence of known or suspected infections, bacteremia, or sepsis requiring antibiotics
- for patients with vasculature that is inadequate for an 8 Fr introducer or catheter advancement without stylet guidance
- when the pump cannot be implanted 2.5 cm or less from the surface of the skin Medtronic Implantable System for Remodulin®
- where skin or soft tissue would heal poorly, increase susceptibility to infections, or is unacceptable for implant of this system
- for patients implanted with leads or catheters (active or abandoned) in the superior vena cava that cannot be removed prior to or at system implant
- for patients who cannot safely tolerate sudden interruptions in treatment.
- in patients whose body size is not sufficient to accept pump bulk and weight.

Remodulin – Limited to use with Remodulin (10 mg/mL concentration). All other drugs are contraindicated. Contraindications relating to the use of Remodulin must be observed. **Blood sampling –** Blood sampling or aspiration through the catheter access port is contraindicated. **Catheter access port kits –** Medtronic catheter access port kits are contraindicated for use with the Implantable System for Remodulin. **Refill kits –** Medtronic refill kits are contraindicated for all catheter access port procedures. **Anticoagulation –** Implant of the infusion system is contraindicated if anticoagulation therapy cannot be managed.

Warnings and Precautions

Comply with all product instructions for initial preparation and filling, implantation, programming, refilling, and accessing the catheter access port of the pump. Failure to comply with all instructions can lead to technical errors or improper use of implanted infusion pumps and result in additional surgical procedures, a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug underdose or overdose. This system is approved for use with Remodulin® (treprostinil) Injection. Non-indicated formulations (including admixtures, compounded drugs, and unapproved drug concentrations) have not been tested with this system. Use of non-indicated drugs or fluids can result in increased risk to the patient, damage to the system requiring surgical replacement, and a loss or a change in therapy that may lead to a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug underdose of the patient. Pocket fill is the improper injection of Remodulin into the subcutaneous tissue, which includes the pump pocket. Pocket fill can result in a site reaction or a clinically significant drug overdose including hemodynamic collapse or death. Inadvertent injection into the catheter access port may result in a clinically significant or fatal drug overdose. During the pivotal clinical trial for the Implantable System for Remodulin, 10% of patients experienced pump failures after 4 years of use. At least 33% of these failures occurring after four years of use resulted in the device failing to deliver Remodulin without corresponding error alarm. The remaining percentage of reported malfunctions occurred with a motor stall alarm that was reported by the patient. Patients who cannot tolerate a sudden cessation of Remodulin therapy may not be appropriate candidates for the Implantable System for Remodulin. Patients with hearing loss may not be able to hear pump error alarms coming from the implanted pump, which may cause delay in therapy if the patient does not hear the alarm and contact the physician in a timely manner. Sources of strong electromagnetic interference (EMI) can affect the operation of a pump, possibly resulting in the following: Patient injury, from heating of the implanted pump resulting in damage to surrounding tissue. System damage, from electrical or mechanical effects that can cause inappropriate device responses or loss of device function, resulting in loss of or change in therapy, which may lead to a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug overdose or underdose. Operational changes to the pump, from strong magnets temporarily or permanently stopping the pump motor or electrical interference causing a pump memory error, resulting in loss of or change in therapy, which may lead to a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug underdose. In the case of a pump memory error or a change to "safe state," reprogramming by a clinician is required. Changes in flow rate, from warming of the implanted pump, resulting in over infusion and a clinically significant or fatal drug overdose.

Potential Adverse Events

Potential adverse events for the Implantable System for Remodulin include: air embolism; allergic or immune system response; anesthesia-related nausea and vomiting; back pain related to lying on the table; catheter dislocation from the vasculature; catheter occlusion; component failure resulting in loss of therapy or inability to program the pump; damage to components; death; disconnection or breakage; erosion; fibrillation and other arrhythmias; hematoma; hemorrhage and exsanguination; improper injection through the catheter access port; infection or sepsis; injection into pocket or subcutaneous tissue; local or systemic Remodulin toxicity and related side effects; low-grade fever; mild or moderate bruising or ecchymosis; nerve damage; overfilling the reservoir; pulmonary arterial

hypertension symptoms—mild exacerbation; pain; pneumothorax and hemothorax; pocket site and incisional pain; poor healing over the pump and catheter incisions; premature end of device service life; programming error; pulmonary embolism or paradoxical embolism; pump inversion or migration; puncture of diaphragm, abdominal organs, or thoracic organs; Remodulin overdose; Remodulin subcutaneous delivery; Remodulin underdose and abrupt cessation; seroma; shoulder pain, discomfort, or stiffness; sleep problems (insomnia); stroke; underdose; venous or arterial dissection or perforation; and venous thrombosis, occlusion, stenosis, insufficiency, or phlebitis.

Prescription Information

Caution: Federal law (USA) restricts this device to sale by or on the order of a physician. See the Implantable System for Remodulin® Technical Manual for detailed information regarding the implant procedure, indications, contraindications, warnings, precautions, and potential complications/adverse events. For further information, please call Medtronic at 1-800-328-2518 and/or consult Medtronic's website at www.medtronic.com.

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 using an external infusion pump with 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 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

- In clinical studies of SC Remodulin infusion, the most common adverse events reported were infusion site pain and infusion site reaction (redness, swelling, and rash). These symptoms were sometimes 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%), rash (14% vs. 11%) 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 of ideal body weight, and monitor closely. 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 or if it affects the breastfed infant or milk production.

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

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