Medtronic

Implantable System for Remodulin®

SynchroMed II 8637P Pump, 8201 Catheter, and 8870 Application Card

Technical Manual

Caution: Federal law (USA) restricts this device to sale by or on the order of a physician.

Contents

1 Explanation of symbols

Table 1. Explanation of symbols on package labeling

Symbol	Explanation
	Open here
	Reorder number
	Serial number
	Consult instructions for use
	Sterilized using ethylene oxide
	Do not reuse
	Use by
	Do not use if package is damaged
	Date of manufacture
	Programmable pump
	Keep away from magnets

2 Implantable System for Remodulin® overview

The Implantable System for Remodulin is a fully implantable system designed to deliver Remodulin® (treprostinil) Injection intravenously for the treatment of patients with pulmonary arterial hypertension (PAH).

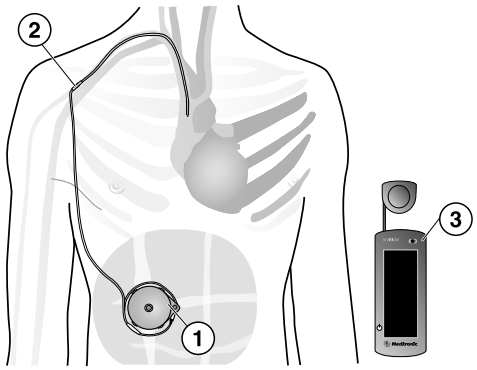
2.1 System description

The Implantable System for Remodulin consists of the following components:

- Medtronic SynchroMed II 8637P Programmable Pump (the “pump”)
- Medtronic 8201 Implantable Intravascular Catheter (the “catheter”)
- Medtronic N’Vision 8840 Clinician Programmer with 8870 Application Card (the “programmer”)

Remodulin (treprostinil) Injection (”Remodulin”) is stored in the pump reservoir and, per a programmed prescription, moves through the pump tubing, the catheter port, and the catheter to the intravascular delivery site. The programmer is a handheld device that is used to review and program pump parameters using telemetry, a radio frequency (RF) communication (see Figure 1). For detailed descriptions of system components, see Chapter 3.

Figure 1. Overview of the Implantable System for Remodulin



1 Pump
2 Catheter
3 Programmer

The pump reservoir may be refilled with Remodulin following a percutaneous procedure using the Medtronic Model 8551 Refill Kit.

2.2 Package contents

The package contents for the pump and catheter are listed in the following sections.

2.2.1 Pump package contents

The pump and accessories are supplied sterile. Each package contains the following items:

- pump
- 22-gauge needle (black sheath)
- 24-gauge needle (purple sheath)
- product literature

2.2.2 Pump patient identification card and registration

A patient identification card is packaged with this device. Advise the patient to carry the identification card at all times.

The patient identification card packaged with the device is temporary; a permanent card is mailed to the patient when Medtronic receives the registration form.

The implant registration form registers the device warranties and creates a record of the device in the Medtronic implant data system.

2.2.3 Catheter package contents

The catheter and accessories are supplied sterile. Each package contains the following items:

- catheter with anchoring sleeve
- sutureless connector
- vein lifter
- retention sleeve
- product literature

2.3 Compatible components

The following components are compatible with the Implantable System for Remodulin:

- Medtronic Model 8551 Refill Kit
- Medtronic Model 8540PAH Catheter Patency Kit
- Medtronic Model 8590 Mesh Pouch Accessory Kit (optional)

2.4 Contact information

Use the following contact information when you have questions.

United Therapeutics Technical Support Services – 1-877-UNITHER (1-877-864-8437)

Medtronic website – www.medtronic.com

Remodulin website – www.remodulin.com

3 Implantable System for Remodulin® components

The 8637P pump, the N'Vision Model 8840 Clinician Programmer with Model 8870 Application Card, and the Model 8201 Catheter comprise the Implantable System for Remodulin.

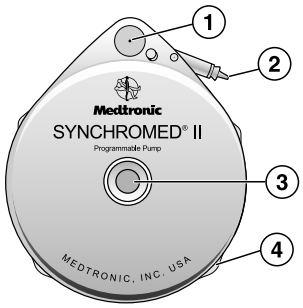
3.1 8637P Pump

The 8637P implantable programmable pump is part of an infusion system that stores and delivers a prescribed drug to a specific site.

3.1.1 Pump description

The catheter connects to the pump catheter port. The pump is anchored in the pump pocket using the suture loops located on the outside of the pump (see Figure 2).

Figure 2. Pump exterior view

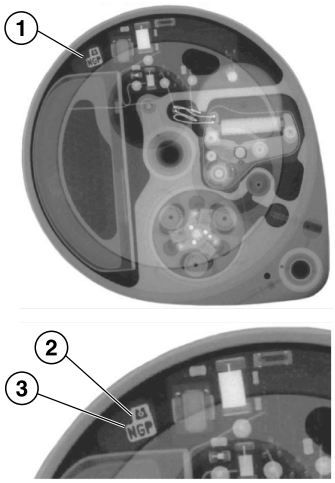


1 Catheter access port
2 Catheter port on the pump
3 Reservoir fill port
4 Suture loop

The drug is stored in the pump reservoir. Per a programmed prescription, the drug moves from the pump reservoir through the pump tubing, the catheter port, and the catheter to the infusion site. The catheter access port (CAP) can be used to assess catheter patency using a Model 8540PAH Catheter Patency Kit. The catheter access port allows entry of a 24-gauge noncoring needle to prevent accidental injection during refill procedures. The refill procedure uses a 22-gauge noncoring needle supplied in the refill kit.

The manufacturer and model code recorded on a radiopaque identifier are visible using standard x-ray procedures (see Figure 3).

Figure 3. Pump x-ray image



1 Radiopaque identifier
2 Medtronic symbol
3 Medtronic designator

3.1.2 Pump specifications

Table 2. Shipping and operating values for the pump

	Shipping	**Operating**
Fluid in reservoir	Sterile water	—
Shipping flow rate	0.006 mL/day	—
Infusion modes	Shelf state	Simple continuous Priming bolus Minimum rate Stopped pump
Alarms		
Critical alarm Non-critical alarm	Disabled Disabled	Enabled with an interval programmed Enabled with an interval programmed

Note: The pump does not include an occlusion alarm notification.

Note: Alarms do not sound in all conditions of pump failure.

Table 3. Specifications for the pump

	8637P-40
Pump	
Thickness (including septum) Mass (empty/full) Displacement volume Diameter (including CAP)	26.1 mm 175/215 g 118 mL 87.5 mm
Pump reservoir	
Volume Residual volume Fill volume at shipping	40.0 mL 1.4 mL 37.5 mL
Pump tubing	
Volume	0.25 mL
Reservoir fill port	
Septum puncture life	500 punctures
Catheter access port	
Prime volume Septum puncture life	0.14 mL 500 punctures
Therapeutic programmable flow rates	
Maximum[a] Minimum[a]	5.76 mL 0.048 mL
Bacterial retentive filter	
Pore size	0.22 µm (micron)
Power source	
Battery Longevity	Lithium hybrid cathode Rate dependent (see Figure 4)
Radiopaque identifier	NGV
Reservoir pressure	20.68 kPa to 34.75 kPa

[a] Actual limits depend on pump calibration constant and selected infusion mode.

Table 4. Material of components in the sterile package

Component	**Material**	**Material contacts human tissue**	**Material contacts drug**
Pump			
Exterior	Titanium	Yes	No
Reservoir	Titanium	No	Yes
Reservoir valve	Titanium	No	Yes
Tubing	Silicone rubber	No	Yes
Reservoir fill port septum	Silicone rubber	Yes	Yes

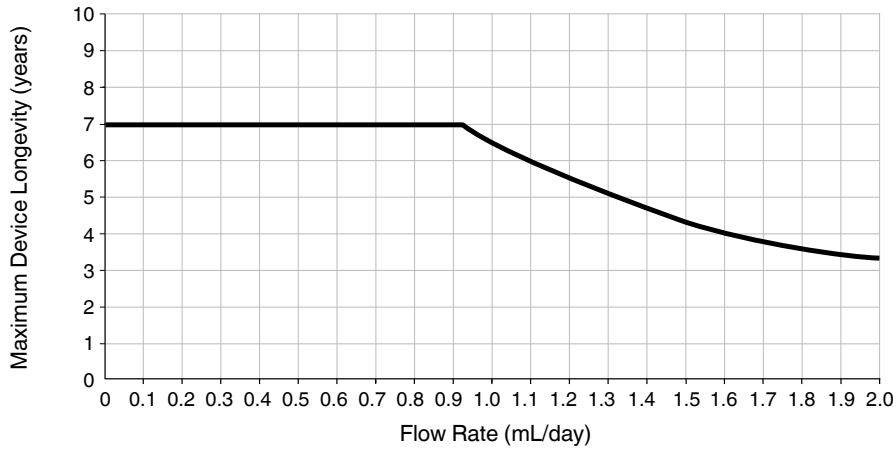
Table 4. Material of components in the sterile package (continued)

Component	Material	Material contacts human tissue	Material contacts drug
Catheter access port septum	Silicone rubber	Yes	Yes
Catheter port	Titanium	Yes	Yes
Bacterial retentive filter	Polyvinylidene-fluoride	No	Yes
Suture loops	Titanium	Yes	No
Propellant	Inert gas	No	No
Needles	Stainless steel	Yes	Yes

3.1.3 Pump longevity

Pump longevity is a function of flow rate. Flow rates affect the battery voltage and motor revolutions (see Figure 4).

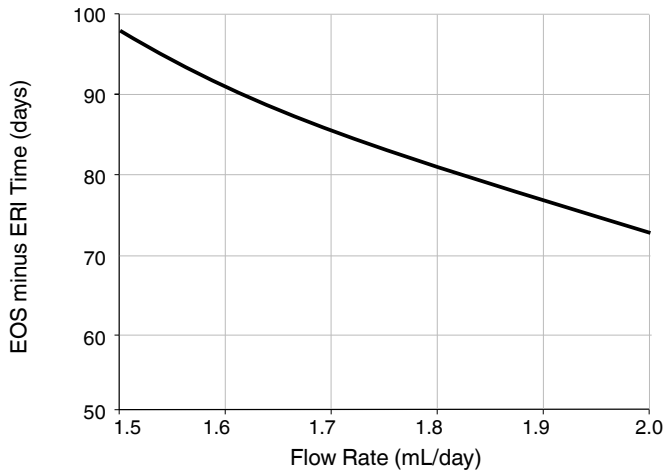
Figure 4. Maximum pump longevity



Note: This graph shows that maximum pump longevity is lower at high flow rates.

Pump longevity is the calculated number of service months remaining based on actual usage rates.[1] An elective replacement indicator (ERI) message displays on the programmer when the pump nears the end of its service life (EOS). At ERI, the pump continues to operate within specifications. The ERI thresholds allow the pump to operate for a minimum of 90 days, at rates up to 1.5 mL/day, between ERI activation and EOS. At flow rates faster than 1.5 mL/day, the time from ERI to EOS may be less than 90 days, as shown in Figure 5. When activated, ERI is date stamped and displayed by the programmer after interrogating the pump. The EOS activation indicates the pump has reached the end of its service life. At EOS, the pump stops, but telemetry is available until the pump battery is depleted.

Figure 5. ERI and EOS



3.1.4 Initial flow rate accuracy

The flow rate accuracy of the pump at manufacture is within ±14.5% of the programmed flow rate at 0.048-24 mL/day, 37°C, 50% reservoir volume, and 300 m above sea level. Measurement error, fluid volume, and changes in environmental conditions (for example, body temperature and atmospheric pressure) all affect the flow rate. The effects of these changes on flow rate are cumulative if the conditions exist simultaneously.

[1] Device longevity sources include battery life (voltage), device life (years), and motor life (revolutions).

3.1.4.1 Accuracy changes over time

Warning: To maintain flow rate accuracy, program the SynchroMed II 8637P Pump to alarm before the volume of drug remaining in the pump reservoir decreases below 1.0 mL. At volumes less than 1.0 mL, flow rate decreases rapidly and stops as the volume reaches 0 mL. This can result in underinfusion and a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug underdose.

The accuracy ratio was tracked at refills in the DelIVery for PAH clinical study. The accuracy ratio formula is provided in Figure 6.

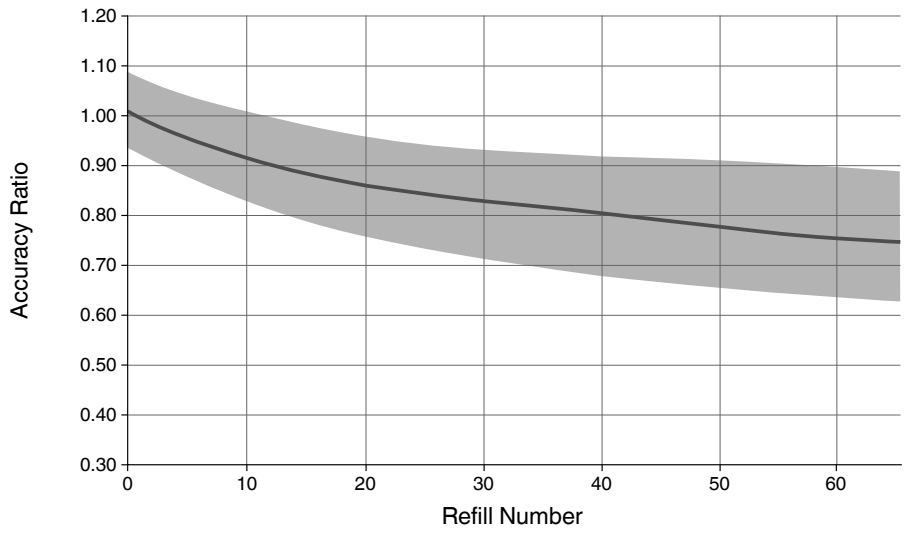
Figure 6. Accuracy Ratio formula

$$\textit{Accuracy Ratio} = \frac{\textit{Previous fill volume - Actual removed volume}}{\textit{Previous fill volume - Expected removed volume}}$$

The Previous fill volume is the volume injected into the pump at the last refill. The Actual removed volume is the volume of drug removed from the reservoir at the current refill. The Expected removed volume is the programmer-indicated volume of drug remaining in the reservoir at the current refill.

Based upon the accuracy ratio data from the study, it has been determined that over a period of time (months to years), the accuracy ratio of the ISR gradually decreases. The decrease is due to an equilibration of gas pressures within the motor chamber. The clinical data, mathematical modeling, and bench testing indicate that over the expected longevity of the pump, the accuracy ratio will decrease and plateau at approximately 0.8. The expected accuracy ratio of the ISR for a 40 mL refill volume is depicted in Figure 7.

Figure 7. Implantable System for Remodulin expected accuracy ratio for a 40 mL refill volume. The shaded area represents the DellVery for PAH clinical trial refill accuracy data (95/95% tolerance interval of the exponential data model).



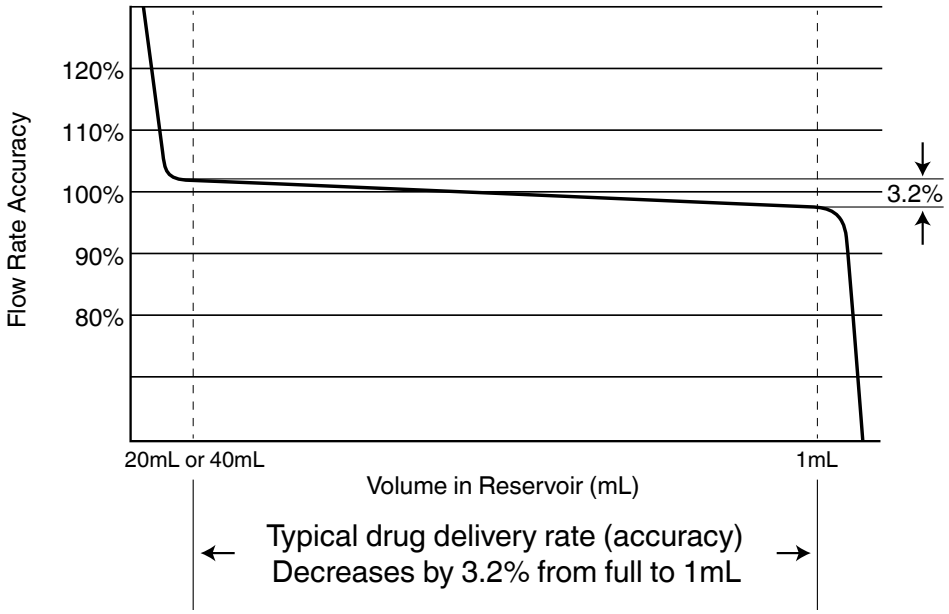
Note: This observed decrease in accuracy ratio only applies to the Implantable System for Remodulin.

The accuracy ratio based on clinical measurements can vary due to measurement error (for example, syringe measurement accuracy, human error, and the volume of fluid in the extension tubing and filter).

3.1.4.2 Fluid volume

The flow rate of the pump varies slightly with the volume of fluid in the pump reservoir. The pump flow rate decreases gradually as the reservoir empties and approaches 1 mL. As the reservoir volume decreases from 1 mL to 0 mL, the pump flow rate decreases rapidly then stops. Therefore, the pump should be refilled prior to reaching 1 mL or less. On average, the flow rate decreases by about 3.2% as the volume is reduced from full to a volume of 1 mL. The useable volume is the reservoir volume minus 1 mL (see Figure 8).

Figure 8. Flow rate accuracy as a function of fluid volume in reservoir



3.1.4.3 Implant time

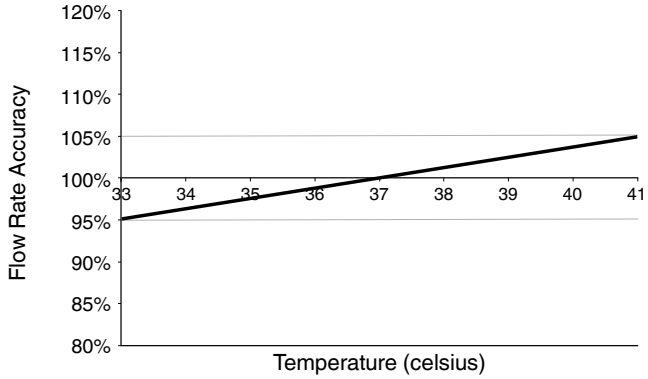
In the DelIVery for PAH clinical trial, a trend was seen of more drug removed from the pump at refill than expected (less drug delivered than expected). The ratio of actual versus expected drug delivered at refill (refill accuracy ratio) decreased as the number of refills increased. See Figure 62 for the DelIVery for PAH clinical trial flow rate accuracy data (refill accuracy ratio).

3.1.5 Environmental conditions

3.1.5.1 Body temperature

The flow rate of the pump varies with body temperature. The flow rate increases as the temperature increases above 37°C and decreases as the temperature decreases below 37°C (see Figure 9).

Figure 9. Flow rate accuracy as a function of temperature (typical effect)

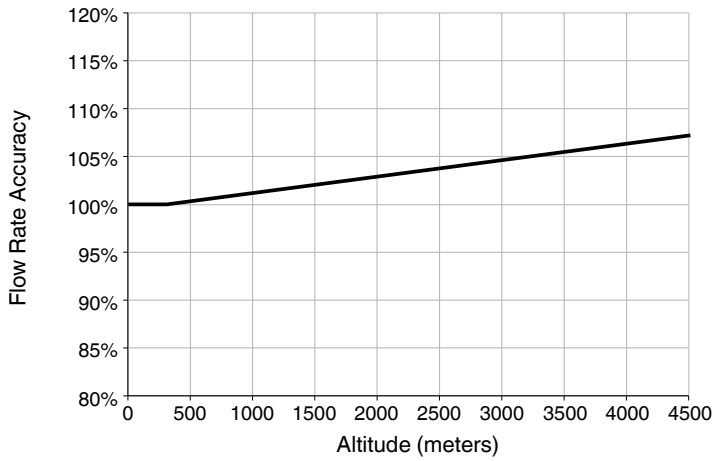


3.1.5.2 Atmospheric pressure

Patients living or traveling at altitudes above sea level (for example, airline flights, mountain climbing) are exposed to lower atmospheric pressures. Within days of exposure to the lower pressures, the flow rate of the pump can increase and then stabilize at the higher flow rate. In circumstances where a potential increase in flow rate may pose a risk to a patient, reprogramming the infusion prescription offsets this higher flow rate (see Figure 10).

In rare instances, exposure to the lower atmospheric pressure can cause the pump to exceed the programmed flow rate by more than 14.5% while the patient is exposed to the lower pressure. Consider changes to pump programming for patients exposed to lower pressures.

Figure 10. Flow rate accuracy as a function of altitude (typical effect)



3.2 FCC Requirements

This device complies with Part 15 of the FCC Rules. Operation is subject to the following two conditions: (1) this device may not cause harmful interference, and (2) this device must accept any interference received, including interference that may cause undesired operation.

Caution: Do not modify the pump without approval of Medtronic. Modifying the device without the approval of Medtronic could void the user's authority to operate the equipment.

3.3 N'Vision Model 8840 Clinician Programmer with Model 8870 Application Card

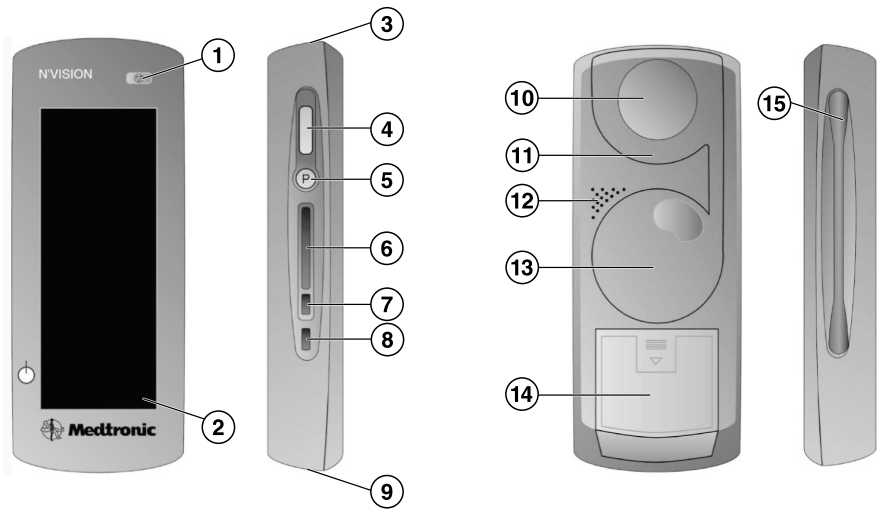
The programmer is used to review and program pump parameters using telemetry, a radio frequency (RF) communication. The examples of the programmer screen images in this manual are provided for reference only and may not match the final software.

3.3.1 Programmer description

The programmer (see Figure 11) with application card is a handheld device for programming Medtronic devices for drug therapies.

If using a programmer for the first time, refer to the setup instructions on the Getting Started card that is packaged with the programmer. Refer to the N'Vision Clinician Programmer 8840 with software 8870 manual for basics about the operation of the programmer and how to interface with the programmer. Instructions specific to the 8870 software application for the Implantable System for Remodulin are included in this manual.

Figure 11. Programmer components



1 Therapy stop key
2 Touchscreen display
3 Infrared port
4 Scroll wheel
5 Programming key
6 Application card port
7 Application card ejection key
8 Power key
9 Expansion port
10 Magnet slot
11 Programming head
12 Speaker
13 Cable reel
14 Battery compartment
15 Touch pen storage

Caution: Do not use the expansion port. The expansion port is a testing port used by Medtronic personnel. Connecting any equipment to this port may damage the programmer.

- Therapy stop key – Initiates the steps to program the pump to Minimum Rate when the Drug Delivery Desktop screen is displayed. Use of this key is not recommended for use with Implantable System for Remodulin. For information on programming the pump to Minimum Rate, see Section 16.2 .
- Touchscreen display – Programmer touchscreen for display and data input
- Infrared port – Allows communication with compatible printers or devices
- Programming key – Depressing the key initiates interrogation or programming
- Application card port – Slot for the application card
- Application card ejection key – Ejects the application card from the programmer
- Power key – Turns the programmer on and off; reactivates the programmer after Standby mode
- Expansion port – Do not use; currently only used for Medtronic testing
- Magnet slot – Holds the Model 8529 magnet (the Model 8529 magnet is not used for the Implantable System for Remodulin)
- Programming head – Allows the programmer to communicate with the device
- Cable reel – Stores a 1 m extendable cable that connects the programming head to the programmer
- Speaker – Programmer speaker
- Battery compartment – Contains the programmer batteries
- Touch pen – Use to enter data on the touchscreen

3.3.2 Software navigation, status, and data entry

Use the touchscreen to navigate through the application, display status, and enter data. When navigating or entering data, use the pointed end of the touch pen to make contact with the touchscreen. Do not use sharp objects such as pencils, pens, or paper clips on the touchscreen. Only use the touch pen to make contact with the touchscreen.

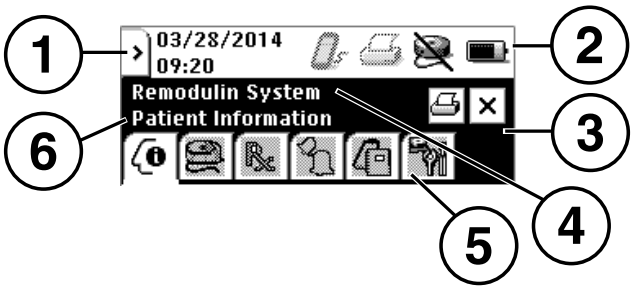
Caution: If touch pen contact with the touchscreen results in a different function, action, or therapy than expected, calibrate the touchscreen.

3.3.2.1 Navigation, status buttons and icons

Navigation and status buttons and icons perform the following functions (see Figure 12):

- Status bar – Displays system date and time as well as status of selected functions and components
- Slider bar – Provides access to programmer information, system settings, and accessories
- Title bar – Displays application name, active screen tab name, and access to selected functions
- Screen tabs – Provides access to programmer screens

Figure 12. Navigation and status buttons and icons



1 Slider bar
2 Status bar
3 Title bar
4 Implantable System for Remodulin identifier
5 Screen tabs
6 Screen identifier

Note: If a value or a button is grayed out, that option is not currently available.

3.3.2.2 Status bar

The status bar shows the status of peripheral devices, the programming head, Demo mode, and the programmer battery. See Table 5 for descriptions of the status bar icons.

Table 5. Descriptions of the status bar icons

Nontelemetry communication port			
	Nontelemetry communication is active		Nontelemetry communication is inactive
Printer			

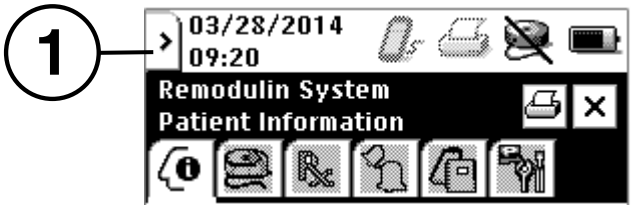
Table 5. Descriptions of the status bar icons (continued)

Nontelemetry communication port			
	Printing		Printing error
	Printing inactive		
Programming head			
	Programming head present		Programming head not present
	Communication established between programming head and device		No communication between programming head and device
	Magnet present on programming head		Magnet present; telemetry successful
	Magnet present; telemetry not successful		
Programmer battery			
	High battery status		Medium battery status
	Low battery status		End of service (EOS) battery status (blinking)

3.3.2.3 Slider bar

The slider bar provides access to programmer information, operating system and display settings, and printer and calculator functions. The slider bar can be accessed anytime during a programming session by selecting the slider bar on the status bar (see Figure 13).

Figure 13. Slider bar



1 Slider bar

Select the slider bar to access the following buttons (see Table 6):

Table 6. Slider bar buttons with descriptions

Button	Description
Information button	
	Displays the names, model numbers, and version numbers for programmer, application, and associated software and peripheral devices
Settings button	
	• Adjusts the display contrast • Adjusts the speaker volume • Adjusts the key click • Calibrates the touchscreen
Localization	
	• Selects the language preference • Selects the date format • Selects the decimal format • Sets the date and time
Session Data Manager	
	• Prints the session data reports • Views the session data reports • Deletes the session data reports
Calculator	
	Accesses the calculator

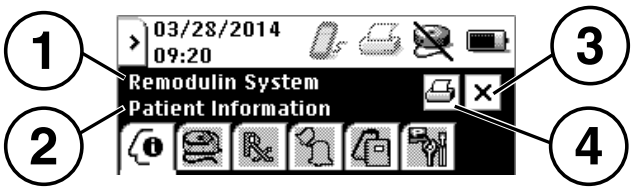
Table 6. Slider bar buttons with descriptions (continued)

Button	Description
Exit application	
	Returns to the Application Selection screen to select a new application

3.3.2.4 Title bar

The title bar displays the application name and active screen tab name. The title bar also provides access to the print and exit application functions (see Figure 14).

Figure 14. Title bar



1 Application name
2 Active screen tab name
3 Exit application
4 Print button

3.3.2.5 Screen tabs

The screen tabs provide access to the programming functions. See Table 7 for a description of each screen tab.

Table 7. Screen tab descriptions

Screen tab	Description
	• Interrogate the pump • Enter patient identification information
	• Display pump model number and serial number • Enter or display catheter model number • Enter or display implanted catheter length
	• Enter or display drug information • Enter or display dosing information • Program infusion modes • Program infusion boluses

Table 7. Screen tab descriptions (continued)

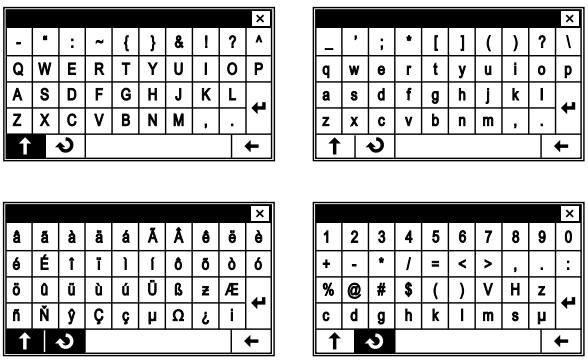
Screen tab	Description
	• View estimated time until ERI • Program Low Reservoir Alarm • Program alarm intervals
	• Update the pump • Display new pump settings after update
	• Access alarm test • Access event logs • Stop pump permanently

3.3.2.6 Data entry

Enter data using by one of the following methods on the touchscreen:

- Drop-down list – A list of values appears when the touch pen contacts the arrow on the right side of a drop-down list. Select a value or entry.
- Input box – Select a value by contacting the touch pen to an input box.
- Keyboard – Four standard keyboards are available (see Figure 15). The keyboard appears when the touch pen contacts an input box that requires alphanumeric input. Select a character to enter data.

Figure 15. Programmer keyboards



Access the keyboards by selecting the following buttons:

– Straight arrow – Select the straight arrow key to change between uppercase, lowercase, international, or special character keyboards.

– Circular arrow – Select the circle arrow key to change between uppercase or lowercase keyboards and international or special character keyboards.

- Numerical entry screen – The screen appears when the touch pen contacts an input box that requires a value. To enter a value, perform the following steps:
  1. Select the position of the digit to be entered.
  2. Select a value that is not grayed out on the top line for each digit. As the value is entered, the position automatically moves to the next digit to the right.
  3. Select the OK button to accept the new value and close the numerical entry screen, or select the Cancel button to close the numerical entry screen without changing the value.

     If the OK button is grayed out and unavailable, then a change that was made to a digit results in an unacceptable value. Digits must be re-entered until an acceptable value is obtained.

3.4 8201 Catheter

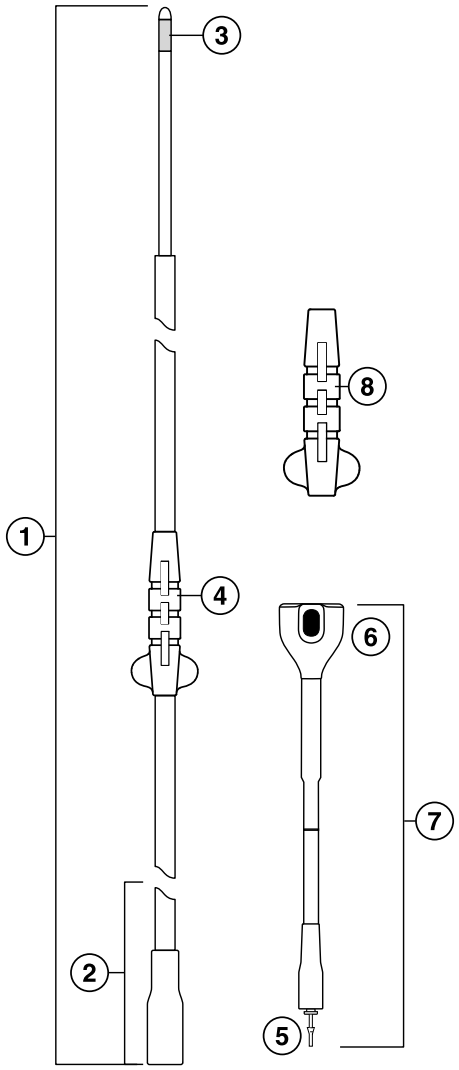
The catheter and the sutureless connector are part of the Medtronic Implantable System for Remodulin that store and deliver Remodulin® (treprostinil) Injection into the bloodstream.

3.4.1 Catheter description

Remodulin is released through a one-way valve (sleeve valve) located at the distal (cardiac) tip of the catheter (see Figure 16). The sleeve valve is designed to minimize blood ingression into the catheter lumen and precludes aspiration of blood from the catheter and the catheter access port.

The catheter is made of radiopaque silicone with enhanced radiopacity at the distal tip.

Figure 16. Catheter with the sutureless connector



1 Catheter body
2 Catheter connector
3 Sleeve valve
4 Anchoring sleeve
5 Sutureless connector pin
6 Sutureless pump connector
7 Sutureless connector
8 Retention sleeve

3.4.2 Catheter accessories and descriptions

Anchoring sleeve – The anchoring sleeve secures the catheter to decrease the risk of catheter migration. The anchoring sleeve is designed to decrease the risk of damage to the catheter body caused by tight sutures.

Sutureless connector – The sutureless connector is the proximal portion of the catheter, which joins the catheter to the pump at the catheter port. The connector pin joins the distal portion of the catheter to the sutureless connector, and the sutureless pump connector joins the sutureless connector to the pump.

Vein lifter – The vein lifter facilitates introducer insertion into a vein.

Retention sleeve – The retention sleeve is used when additional sutures are desired to secure the catheter.

3.4.3 Specifications for the catheter with the sutureless connector (nominal)

Description	Value
Length	80 cm (31.5 in)
Introducer size	8 Fr or larger (if using a valved introducer, use a 9 Fr or larger transvalvular introducer TVI tool)
Tunnel tool size	Inner diameter 14 Fr (4.6 mm / 0.182 in) or larger
Outer diameter	2.4 mm (0.094 in)
Inner diameter	0.5 mm (0.021 in)
Catheter volume (per length unit)	0.0022 mL per cm
Total catheter volume	176 uL
Material	Radiopaque silicone – inner tube
	Silicone – outer tube
	Graphite – inner surface between the sleeve valve and the catheter body

4 Indications, contraindications, and adverse events

Warning: 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.

Indications are listed for the system as a whole. The contraindications are listed by category. The potential adverse events are listed by component (pump and catheter) and procedure (implant and refill).

4.1 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 8551 Refill Kit is intended for use in refilling the Medtronic implantable programmable infusion pumps with the exception of Medtronic MiniMed infusion pumps.

4.2 System 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

- 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.

4.3 Adverse events

The following table summarizes the potential adverse events related to Implantable System for Remodulin. The check marks indicate the components and procedures where the individual adverse events may occur (see Table 8). Refer to the Remodulin drug labeling for adverse events related to Remodulin.

Table 8. Potential adverse events for the Implantable System for Remodulin

Adverse event	Pump	Catheter	Implant procedure	Refill procedure
Air embolism			x	
Allergic or immune system response[a]	x	x	x	x
Anesthesia-related nausea and vomiting			x	
Back pain related to lying on the table			x	
Catheter dislocation from the vasculature		x	x	
Catheter occlusion		x		
Component failure resulting in loss of therapy or inability to program the pump	x	x		
Damage to components	x	x	x	x
Death	x	x	x	x
Disconnection or breakage	x	x	x	x

Table 8. Potential adverse events for the Implantable System for Remodulin (continued)

Adverse event	Pump	Catheter	Implant procedure	Refill procedure
Erosion	x	x	x	x
Fibrillation and other arrhythmias		x	x	
Hematoma	x	x	x	x
Hemorrhage and exsanguination			x	
Improper injection through the catheter access port			x	x
Infection or sepsis	x	x	x	x
Injection into pocket or subcutaneous tissue				x
Local or systemic Remodulin toxicity and related side effects	x	x	x	x
Low-grade fever			x	
Mild or moderate bruising or ecchymosis			x	x
Nerve damage			x	
Overfilling the reservoir			x	x
Pulmonary arterial hypertension symptoms—mild exacerbation			x	
Pain	x	x	x	x
Pneumothorax and hemothorax			x	
Pocket site and incisional pain	x		x	
Poor healing over the pump and catheter incisions	x	x	x	
Premature end of device service life	x			
Programming error	x		x	x
Pulmonary embolism or paradoxical embolism		x	x	
Pump inversion or migration	x		x	
Puncture of diaphragm, abdominal organs, or thoracic organs			x	
Remodulin overdose	x	x	x	x
Remodulin subcutaneous delivery	x	x	x	x
Remodulin underdose and abrupt cessation	x	x	x	x
Seroma	x	x	x	x
Shoulder pain, discomfort, or stiffness			x	
Sleep problems (insomnia)			x	
Stroke		x	x	
Underdose	x	x	x	x

Table 8. Potential adverse events for the Implantable System for Remodulin (continued)

Adverse event	Pump	Catheter	Implant procedure	Refill procedure
Venous or arterial dissection or perforation			x	
Venous thrombosis, occlusion, stenosis, insufficiency, or phlebitis		x	x	

[a] For a list of materials used in the system see Section 3.1.2 and Section 3.4.3.

4.4 Considerations prior to implant

The background information on the Implantable System for Remodulin presented here assists clinicians in assessing risk associated with the system.

Implantable System for Remodulin – The system consists of the 8637P pump, the N'Vision Model 8840 Clinician Programmer with Model 8870 Application Card, and the Model 8201 Catheter.

As with any programmable electronic or mechanical system, failure may occur that may be transparent to the patient or may affect performance. The infusion pump includes features to detect various levels of system failures and alarm notifications for the patient. It also includes more detailed information for troubleshooting for the clinician. However, the patient may experience symptoms of overdose, underdose, or abrupt cessation of therapy that may require unplanned surgical procedures to reposition or replace system components or the entire system. Consequences of such situations should be considered for use of this system with each individual patient.

In addition to these concerns, the decision to implant the Implantable System for Remodulin should include the patient's anatomy, the intended location of the pump, and considerations for pump volume and size, as well as catheter length. Location of the pump in the patient's anatomy may make future refills difficult should the pump be located in a place that it is difficult to access or where it migrates or flips. Other considerations include patient's condition, comorbidities, concurrent systems, procedure-related issues that may occur with an implant, and long-term need.

For patient safety, and appropriate utilization of the system, the following are recommended:

- Select patients who have responded to and tolerated Remodulin for at least 30 days.
- Select patients who can have their anticoagulation therapy managed to permit safe device implantation.
- Do not implant patients who have had a recent infection in the last 60 days requiring antibiotics.
- Do not implant patients who have a recent history of pulmonary embolism in the last 90 days.

- Exclude patients who have increased risk of systemic or soft tissue infections.
- The implant of the pump involves pain, risk of infection, complications from the implant and refill procedures. The external pump can be refilled, have dose adjustments, and be replaced without the patient leaving home. In contrast the Implantable System for Remodulin requires that the patient travel to a specialty center for all adjustments to the treatment with the system.
- Patients who cannot tolerate a sudden cessation of Remodulin therapy may not be appropriate candidates for the Implantable System for Remodulin.

Note: Patients who do not have a monitoring device and therefore do not have the ability to determine if the device is not functioning as expected

Use environment – The Implantable System for Remodulin is designed to operate over a range of operating conditions as outlined in this manual; however, specific environmental or use conditions for each patient, as well as lifestyle and activity levels of daily living, should be included when considering the use of this system for a particular patient.

Clinical management – The Implantable System for Remodulin requires periodic management for monitoring the patient, the infusion system, and the continued delivery of Remodulin. Clinical implant and management of this system requires healthcare providers with the proper level of training and experience and requires that these procedures be performed in a medical facility with proper staffing, monitoring equipment, and emergency life support to address potential clinical situations and emergencies related to this system and the use of Remodulin. Specific clinical situations related to the use of Remodulin and this system may arise that require clinical expertise in the management of PAH patients in normal and emergency situations, medical staffing trained in PAH patient management, and facilities that are equipped to deal with life-threatening situations, including those caused by Remodulin overdose. Of primary concern is the situation that may occur during pump refill where Remodulin is injected into the surrounding tissue. Other situations related to site reactions may occur during a pump refill, during catheter positioning, or with procedures where the system or system components require replacement and drug is unintentionally dispensed into the surrounding tissue. These situations are specifically addressed in the refill procedure as well as in the section dealing with emergency situations related to overdose (see Section 8.2).

The infusion pump requires programming by a trained healthcare provider. Potential errors have been addressed in the design of the user interface, but situations may occur should incorrect values, modes, drug concentrations, or other necessary actions be taken. These may result in unintended programming, resulting in unintended dosing (overdosing, underdosing, or unintended loss of therapy), longevity issues, or issues related to priming or change of concentration procedures. The program application used for the Implantable System for Remodulin includes the available catheter models, drug concentrations, and dosing parameter ranges encountered for this patient population. However, options are

included for other catheters or bolus options, but these require that a Medtronic representative be contacted prior to their use.

The patient's prescribing physician is expected to provide information and instructions to the patient regarding use of the system, limitations for daily living, alert notification, refill notification, identification of overdose, underdose and abrupt cessation, and other patient-specific information.

5 Warnings

Warnings in this chapter apply to the general operation of the system. Warnings that apply to specific steps in the procedure are included in the appropriate instructions. For warnings specific to Remodulin® (treprostinil) Injection, see Section 5.3

5.1 System warnings

Pump failure during clinical trial – 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 those failures occurred after 4 years and resulted in the device failing to deliver Remodulin without a 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 – Patients with hearing loss may not be able to hear pump error alarms coming from the implanted pump. Therapy may be delayed if the patient does not hear the alarm and contact the physician in a timely manner.

User instructions – 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.

Use with Remodulin – This system is approved for use with Remodulin. 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.

Drug incompatibility – This system is approved for use with Remodulin. Do not use drugs or drug mixtures that precipitate in the pump and inhibit pump flow or occlude the catheter (for example, greater than approved concentrations). Do not use drugs or fluids that:

- contain preservatives (for example, sodium metabisulfite) that are known to damage the system
- contain antimicrobials that are known to damage the system
- contain antioxidants that are known to damage the system

- exhibit chemical properties (such as pH ≤3) that are known to damage the system
- break down over time and produce degradation products that are not compatible with the system (for example, diamorphine and diacetylmorphine)

Calibration constant – The calibration constant displayed on the programmer screen after reading the pump status must match the calibration constant printed on the shelf package. If calibration constants differ, contact the appropriate representative listed in Section 2.4. Using an incorrect calibration constant can result in a clinically significant or fatal drug underdose or overdose.

Interrogating and programming the pump – Before interrogating or programming the pump, confirm that the time and date on the programmer are correct. Incorrect time and date can result in incorrect estimated refill dates, which may cause the patient to be underdosed or result in an abrupt cessation of drug delivery to the patient.

Check Event log at every patient visit – At every patient visit, the clinician must review the Event log to check for any pump failures that have occurred since the last visit.

Connections – Firmly secure all connections, including the connections from the catheter to the sutureless connector and from the sutureless connector to the pump. Failure to secure connections can allow drug to leak onto the surrounding skin and may result in overdose, site reaction, or underdose.

Contrast medium – Do not inject any contrast medium into the pump reservoir or the catheter access port. Injecting contrast medium into the pump reservoir can impair the pump. The catheter cannot be aspirated so injecting contrast medium into the catheter access port would result in an overdose.

Handling the pump – Handle the pump with care. Do not drop or damage the pump. Implanting a pump that has been dropped or damaged can result in unintended therapy, including a potential drug overdose or underdose of the patient, and may require additional surgery to replace the pump.

Injection error during a pump refill procedure – Be certain that you are accessing the correct port when injecting fluids into the reservoir fill port of an implanted pump. Always do the following:

- Identify the pump model and the reservoir volume.
- Identify the location of the reservoir fill port.
- Use the instructions, noncoring needles, appropriate template, and other accessories provided in the appropriate kit.
- Verify the location of the correct port during needle insertion according to the instructions provided.
- Refer to the appropriate drug labeling for indications, contraindications, warnings, precautions, adverse events, and dosage and administration information.

- Observe the patient for a minimum of 1 hour after the pump refill procedure for any signs or symptoms that could indicate a pocket fill or any other drug-related adverse event due to the refill procedure. Seek emergency assistance as necessary.

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.

Use of coring needle – Use of a coring needle rather than a noncoring needle during a pump fill may result in damage to the reservoir septum and may cause drug to leak from the septum into the pocket tissue which can result in a site reaction or a clinically significant drug overdose including hemodynamic collapse or death.

Pocket fill – If it is suspected or known that all or part of the drug was injected into the pocket during the refill procedure, monitor the patient closely for signs and symptoms of overdose and seek emergency assistance. Monitor the patient in an appropriate facility for a sufficient amount of time or until the symptoms have resolved. For more information, see Section 8.2.

Therapy discontinuance – Discontinuing therapy by stopping the pump for extended periods or allowing the pump reservoir to empty completely can damage the system and require surgical replacement. To prevent damage to the pump, program the pump to Minimum Rate.

Refill kit components – The appropriate Medtronic refill kit must be used during all refill procedures for Medtronic implantable infusion pumps. Using components other than Medtronic components or a kit other than the appropriate refill kit can damage Medtronic components, requiring surgical revision or replacement, and allow drug leakage into surrounding tissue, resulting in tissue damage or 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 or overdose.

Refill reaction (not pocket fill) – Monitor the patient for one hour after the refill procedure. Refill reactions may occur during needle removal as a result of Remodulin that forms at the needle tip as the needle is retracted from the subcutaneous tissue. This may result in local reactions at the pump refill site and potentially systemic reactions. Local reactions due to side effects of Remodulin may include pain, erythema, and swelling. Systemic reactions due to Remodulin overdose may include flushing, headache, nausea, and hemodynamic changes. Chilling Remodulin is intended to reduce the incidence and magnitude of the refill reaction. Overfilling the pump and failure to close the clamp on the extension line at the end of the refill may increase the likelihood of refill reactions.

Reservoir fill port injections – Do not use excessive force when accessing the reservoir fill port. Excessive force can result in damage to the needle or pump requiring surgical revision or replacement, and leakage into surrounding tissue, resulting in tissue damage or 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 or overdose.

5.2 Catheter warnings

Alcohol contact – Do not expose the sutureless connector catheter component to alcohol or solutions containing alcohol. Alcohol can damage the sutureless connector resulting in drug leakage into surrounding tissue. This may lead to pain, redness, and swelling. Damage to the components can require surgery to repair or replace the components.

Catheter aspiration and blood sampling – Do not attempt to aspirate blood through the catheter access port or the catheter. The one-way valve on the distal end of the catheter is designed to prevent blood from entering the catheter lumen.

Drug aspiration from the catheter – It is not possible to aspirate all of the drug from the lumen. A subsequent injection into the catheter access port or the catheter may result in a fatal overdose because of the residual drug in the catheter.

Catheter in the right atrium – During a system implant or catheter replacement, do not advance the catheter into the right atrium, as atrial fibrillation may occur.

Concurrent devices – Concurrent catheters or leads in the same vessel may adversely affect the performance of the catheter. Concurrent devices increase the risk of thrombus, fibrotic encapsulation, or venous insufficiency and may lead potentially to catheter occlusion and abrupt cessation of drug therapy. Concurrent externalized catheters may increase the risk of infection leading to sepsis.

Contrast agent injection – The catheter has not been tested for use with a radiographic contrast agent. Do not inject radiographic contrast agents through the catheter as they may occlude the one-way valve.

Catheter use – Use of catheters may cause trauma to the heart and vasculature. Do not apply force to the catheter during the implant procedure if significant resistance is encountered. Applying force may injure the patient.

Catheter model number – When implanting a new system or replacing a catheter, confirm that the intended catheter is selected, programmed, and implanted. Selecting an incorrect catheter model number may lead to a potential drug overdose or underdose of the patient.

Handling the catheter – Handle the catheter with care at all times. The distal end of the catheter (closest to the heart) in the region of the one-way valve (black band) can be damaged by mishandling. Do not wipe the catheter; damage may occur. Do not touch or contact the one-way valve as this may cause an inversion of the one-way valve, which may lead to a catheter occlusion and an abrupt cessation of drug delivery.

Heparin and antibiotic solutions – The catheter has not been tested for use after soaking or flushing in heparin or antibiotic solutions. Do not soak or flush the catheter in these substances as they may affect the performance of the one-way valve.

Inspection of catheter and one-way valve – Inspect the catheter and one-way valve for damage and observable defects before implant. Verify that the one-way valve covers the side hole of the catheter and that it does not have any tears or holes. Do not implant the catheter if it is damaged. A damaged catheter may allow blood to enter the catheter valve and occlude the catheter, resulting in reduced or abrupt cessation of drug delivery.

Introducer – The catheter is intended to only be inserted into an 8 Fr introducer. Do not withdraw the catheter relative to the introducer, as this may cause damage or inversion of the one-way valve. Damage or inversion of the one-way valve may possibly lead to catheter occlusion and abrupt cessation of drug delivery.

Stylet – The catheter is not intended for use with a stylet and is not supplied with a stylet. Insertion of a stylet into the catheter lumen may damage the catheter body, damage the one-way valve on the distal end, and/or dislodge and embolize the catheter tip.

Sutureless connector – Verify that the sutureless connector is secured correctly to the catheter and the pump. Failure to connect the sutureless connector securely to the catheter and the pump may allow Remodulin to leak from the junction. If Remodulin leaks from the junction, a localized site reaction may occur.

Catheter access port – Do not flush the catheter access port with Remodulin after it is connected to an implanted catheter. Flushing the catheter access port with the catheter connected can result in a clinically significant or fatal overdose of Remodulin.

System integrity check – Do not perform a system integrity check or flush any fluid into the access port of an implanted system. Remodulin is in the catheter and the catheter access port, and a system integrity check or a fluid flush of the catheter access port may deliver an excess of Remodulin to the patient. This action may cause a life-threatening overdose of the patient.

5.3 Remodulin warnings

Drug quality – Do not use a drug if sterility is questionable, if the drug is cloudy or discolored, if it contains visible particulates, or if it is beyond its labeled shelf life. Using such a drug may cause infection or component occlusion that inhibits drug delivery, resulting in a 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, and require surgical revision or replacement.

Drug information – Refer to the drug labeling for indications, contraindications, warnings, precautions, dosage and administration information, and screening procedures. Refer to the

drug labeling for specific drug underdose or overdose symptoms and methods of management. Failure to refer to the drug labeling can result in inappropriate patient selection and management, inadequate therapy, intolerable side effects, or a clinically significant or fatal drug underdose or overdose. Consider the possibility of a drug error if the patient experiences unusual side effects. Failure to do so can result in misdiagnosis of patient symptoms.

Drug underdose and overdose – Inform patients and caregivers of the signs and symptoms of a drug underdose and overdose. Inform patients and caregivers:

- to be aware and report any unusual signs or symptoms at any time during or after a refill or catheter access port procedure
- to be alert for any burning sensations in the area of the pump pocket during the refill or catheter access port procedure
- to especially watch for signs of underdose and overdose
- to stay alert for signs or symptoms that may indicate changes to their programmed dose
- to seek emergency assistance as necessary

Failure to recognize these signs and symptoms and to seek appropriate medical intervention can result in serious patient injury or death.

Drug overdose symptoms and management – Refer to Chapter 8 and the drug labeling for specific drug overdose symptoms and methods of management.

Drug interaction and side effects – Inform patients of the appropriate warnings and precautions regarding drug interactions, potential side effects, and signs and symptoms that require medical attention. Failure to recognize the signs and symptoms and to seek appropriate medical intervention can result in serious patient injury or death.

Remodulin on the exterior of the pump – Before the pump is implanted in the patient, wipe the exterior of the pump with gauze to remove any Remodulin. Remodulin on the exterior of the implanted pump could cause a local tissue reaction or an overdose of the patient.

Change in Remodulin dose – Do not change the dose of Remodulin without consulting the PAH managing physician. A change in dose may cause a drug overdose or underdose of the patient.

Change in dosing weight – Do not change the dosing weight without consulting the PAH managing physician. The change in dosing weight may cause a drug overdose or underdose of the patient.

5.4 Prime bolus

Priming bolus – Mixing of drug and non-drug (sterile water, saline) fluids occurs at the high flow rate used during a priming bolus. This mixing can result in a period of reduced drug concentration following the priming bolus. This mixing can lead to adverse events involving drug overdose prior to turning off the external line or drug underdose after the external line has been turned off. Follow these guidelines regarding priming bolus and the transition from the external line to the implanted system:

- Perform the Prime for New System Implant procedure under the supervision of a PAH clinician. Closely monitor the patient during the transition of Remodulin delivery from the external line to the implanted system. An overdose or underdose of the patient may occur during this transition and may require medical management of the patient. In the DellVery for PAH clinical study, all patients were monitored overnight in a hospital setting.
- If signs of overdose (identified in Section 8.1.1) occur before the external line is turned off, the external line may be turned off earlier than the calculated time provided by the programmer.
- Based on the therapeutic index of Remodulin and the sensitivity of the patient, some individuals may need additional monitoring until the delivered drug reaches the intended concentration. If signs of an underdose (identified in Section 8.3.1) occur, do not increase the programmed daily dose within the first 72 hours following a priming bolus as the delivered drug may not have reached the intended concentration during this time.

5.5 Physician training

Implantation and system management – Implantation and ongoing system management must be performed by individuals trained in the operation and handling of the system and must be in compliance with procedures described in the appropriate technical instructions. Inadequate training or failure to follow instructions can require surgical revision or replacement, and result in a clinically significant or fatal drug underdose or overdose.

Prescribing – Physicians must be familiar with the drug stability information and must understand the dose relationship to drug concentration and flow rate before prescribing an infusion system. Failure to understand the relationships between concentration, flow rate, dose, and drug stability can result in a clinically significant or fatal drug underdose or overdose.

5.6 Patient activities and information

Change in patient's condition – Provide patients with periodic reminders that they should contact their managing physician if there is any change in their condition and/or symptoms since alarms may not sound in all conditions of pump failure.

Activities involving exposure to high altitudes – Patients who live or travel at high altitudes are exposed to lower air pressures. With continued exposure to lower air pressure, the flow rate of the pump may increase and then stabilize at the higher flow rate. In those circumstances where a potential increase in flow rate may pose a risk for a patient, the infusion prescription can be adjusted to offset the higher flow rate. In rare instances, while the patient is exposed to lower pressures, exposure to lower pressures can cause the flow rate of the pump to exceed the programmed flow rate by more than 14.5%. A change in pump programming can be considered for patients who will be exposed to lower pressures.

Activities involving exposure to high temperatures – Patients should avoid using hot tubs, hot showers, steam rooms, saunas, or tanning beds where the temperature is greater than 39°C (102°F). The flow rate of the pump will vary with body temperature. The flow rate increases as the temperature increases. A significant increase in temperature can result in overinfusion and a clinically significant or fatal drug overdose.

Activities requiring excessive twisting or stretching – Patients should avoid activities that put undue stress on the implanted components of the system. Activities that include sudden, excessive, or repetitive bending, twisting, bouncing, or stretching can damage or dislodge components and require surgical revision or replacement. These activities can also kink or occlude the catheter, resulting in a 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.

Component manipulation by patient (twiddler's syndrome) – Patients should avoid manipulating or rubbing the pump or catheter through the skin. Manipulation can cause skin erosion, component damage, catheter disconnection, kinking, or dislodgement and result in drug leakage into surrounding tissue and tissue damage or a 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 or overdose, and can require surgical revision or replacement. Manipulation may also cause pump inversion, making it impossible to refill the pump.

Elective Replacement Indicator (pump) – Inform patients that the SynchroMed II pump has an Elective Replacement Indicator (ERI) that sounds when the pump is nearing End of Service (EOS). When the ERI sounds, patients must contact their physician to schedule a pump replacement. If the pump is not replaced after the ERI sounds, the pump will reach EOS after 90 days and the pump will stop. A stopped pump results in loss of therapy, which may lead to a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug underdose.

Long-term catheter damage – Inform patients that the catheter is subject to wear. Over time, the component may fail and require surgical revision or replacement. Component failure can result in drug leakage into surrounding tissue and tissue damage or a 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 or overdose.

Medical procedures – Patients should always inform health care professionals that they have an implanted pump before undergoing medical tests or procedures. Failure to inform health care professionals can result in procedural delays, patient injury, component damage that requires surgical revision or replacement, or a clinically significant or fatal underdose or overdose.

Patient travel – Patients should notify their clinicians of any travel plans. Clinicians need this information to coordinate patient care and pump refills and help prevent a 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.

Refill – Patients must return to the clinic for refills at the prescribed times. Failure to return to the clinic for refills at the prescribed times can result in the actual flow rate of the pump being less than expected, resulting in a 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. Failure to return at the prescribed times can also damage the pump, requiring surgical replacement.

Scuba diving or hyperbaric chambers – Patients should not dive below 10 meters of water or enter hyperbaric chambers above 2.0 atmospheres absolute (ATA). Pressures below 10 meters of water (or above 2.0 ATA) could damage the pump, requiring surgical replacement. To minimize damage to the pump when hyperbaric treatment is required, fill the pump to capacity using the appropriate refill kit and maintain the current infusion prescription prior to exposure to hyperbaric conditions. Before diving or using a hyperbaric chamber, patients should discuss the effects of high pressure with their physician. As pressure increases, pump flow decreases. Continuing to increase the pressure will eventually result in a 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.

6 Precautions

Precautions in this chapter apply to the general operation of the system. Cautions that apply to specific steps in the procedure are included in the appropriate instructions.

6.1 Storage

Component packaging – Before shipment the components in the sterile package were sterilized by the process indicated on the package label. Do not use or implant a component if the following circumstances have occurred:

- The storage package or sterile seal has been pierced or altered because component sterility cannot be guaranteed and infection may occur. Contact a Medtronic representative if the seal or package is damaged.
- The component shows signs of damage because the component may not function properly.
- The use-by date has expired because component sterility cannot be guaranteed and infection may occur; also, device battery longevity may be reduced and may require early replacement.

Pump resterilization – The pump is for single use only and is not intended to be resterilized. The pump is sterilized with ethylene oxide before shipment. Do not resterilize the pump. Do not steam or flash autoclave the pump. At high temperatures, the pump can explode, resulting in equipment damage or personal injury.

Catheter resterilization – The catheter is for single use only and is not intended to be resterilized. The catheter is sterilized with ethylene oxide before shipment. Do not resterilize the catheter because resterilization may damage the catheter. A reused catheter may introduce an infection or other communicable diseases to the patient, or the catheter's performance may be compromised or insufficient.

Programmer or programming head resterilization – Do not sterilize any part of the programmer. The programmer and the programming head are not designed to be sterilized. Sterilization may damage the programmer or the programming head.

Single use only – Do not reuse any component. Components are intended for single use only. Reusing components can result in inadequate therapy and an increased risk of infection.

Storage temperature: catheters – Do not store or transport the catheter and accessories above 40°C (104°F) or below –34°C (–29°F). Temperatures outside this range can damage components.

Storage temperature: pumps – Do not store or transport the pump above 43°C (110°F) or below 5°C (40°F). Temperatures outside this range can damage components.

6.2 System implant

Compatibility, all components – Follow these guidelines when selecting system components:

- Medtronic components: For proper therapy, use only components that are compatible with the appropriate indication.
- Non-Medtronic components: No claims of safety, efficacy, or compatibility are made with regard to the use of non-Medtronic components with Medtronic components. Refer to the non-Medtronic documentation for information.

Component handling – Handle the implantable components of this system with extreme care. These components may be damaged by excessive traction or sharp instruments, requiring surgical replacement. Refer to the appropriate implant manual for additional instructions.

Replacement surgery – Patient management should be increased following pump or catheter replacement to ensure quick response to any signs of underdose or overdose.

Aseptic technique – Use strict aseptic technique when accessing the reservoir fill port or the catheter access port of an implanted pump. Failure to use aseptic technique can contaminate fluids or tissues and result in local or systemic infection.

Infection – Use extreme caution when accessing the reservoir fill port or catheter access port of the implanted pump if local or systemic infection is suspected. Avoid contaminating the system or further spreading the infection. Local or systemic infection may require pump revision or removal.

6.3 Clinician programming

Clinician programmer interaction with a cochlear implant – When the patient has a cochlear implant, minimize or eliminate the potential for unintended audible clicks during telemetry by keeping the external portion of the cochlear system as far from the programming head as possible or by turning off the cochlear implant during programming.

Clinician programmer interaction with flammable atmospheres – The programmer is not certified for use in the presence of a flammable anesthetic mixture with air or with oxygen or nitrous oxide. The consequences of using the programmer near flammable atmospheres are unknown.

Clinician programmer interaction with other active implanted devices – When a patient has a programmable pump and another active implanted device (for example, a pacemaker, a defibrillator, or a neurostimulator):

- the radio frequency (RF) signal used to program either device can reset or reprogram the other device.
- the magnet in a cardiac programmer may temporarily stop the pump.

To verify that inadvertent programming did not occur, clinicians familiar with each device should check the programmed parameters of each device before the patient is discharged from the hospital and after each programming session of either device (or as soon as possible after these times).

Also, inform patients to contact their physician immediately if they experience symptoms that could be related to either device or to the medical condition treated by either device.

Telemetry signal disruption from EMI – Do not attempt telemetry near equipment that may generate electromagnetic interference (EMI). EMI can interfere with programmer telemetry. If EMI disrupts programming, move the programmer away from the likely source of EMI. Examples of sources of EMI are magnetic resonance imaging (MRI), lithotripsy, computer monitors, cellular phones, motorized wheelchairs, x-ray equipment, and other monitoring equipment. Interrupting telemetry can result in incorrect or incomplete programming.

6.4 Interaction with other cardiac procedures

Atrial septostomy and right heart catheterization – Use care when introducing a right heart or atrial septostomy catheter into the SVC and past the implanted Remodulin catheter and sleeve valve. The patient's vasculature, interference with the Remodulin infusion catheter, potential for vasculature insufficiency, and other related risks of the procedure, including thrombosis and infection, need to be considered.

7 Drug information

Warning: 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.

The Implantable System for Remodulin is approved for use with a Remodulin concentration of 10 mg/mL.

7.1 Drug stability

Testing has indicated that a Remodulin concentration of 10 mg/mL is stable for 112 days (16 weeks) with the Implantable System for Remodulin. Stability is defined as greater than or equal to 90% of initial concentration. Testing has also indicated that a Remodulin concentration of 10 mg/mL is compatible with the Implantable System for Remodulin.

Refer to the Remodulin labeling for complete prescribing information, including indications, contraindications, warnings, precautions, and adverse events.

7.2 Drug refill information

The maximum refill interval for the Implantable System for Remodulin is 112 days (16 weeks). Before the end of the 112 days, all remaining Remodulin in the pump reservoir must be removed and replaced with new Remodulin.

Refer to Chapter 13 for refill instructions.

8 Emergency procedures

A list of symptoms and procedures for correcting Remodulin® (treprostinil) Injection overdose, suspected pump pocket fill, and abrupt cessation or sudden large reduction of Remodulin are presented in this chapter. The emergency procedure to empty the pump reservoir is also included.

8.1 Remodulin overdose

A large overdose of Remodulin may result in a clinically significant drug overdose and may result in hemodynamic collapse or death. Consult the patient's medical record or consult with the patient's physician to confirm the drug concentration in the pump reservoir.

8.1.1 Remodulin overdose symptoms

The potential Remodulin overdose signs and symptoms include, but are not limited to, the following:

- flushing
- headache
- hypotension
- nausea
- vomiting
- diarrhea

8.1.2 Remodulin overdose procedure

If an overdose of Remodulin is suspected, perform the following actions, as necessary:

- Stabilize and medically manage the patient.
- Immediately contact a physician experienced with Remodulin injection, preferably the physician managing the therapy for the patient in question.
- Regularly assess the vital signs of the patient.
- Admit the patient to a monitored hospital setting, such as an intensive care unit or a step-down unit.

- Determine if the N'Vision Pump Programmer is available.
  - If the programmer is available, interrogate the pump and verify pump settings and function. Program the pump to Minimum Rate, if necessary.
  - If the programmer is not available, empty the pump reservoir to stop the drug flow (see Section 8.4).

Notes:

- Medtronic does not recommend running an empty pump or stopping a pump for more than 48 hours.
- Refer to the drug manufacturer's package insert for a complete list of indications, contraindications, warnings, precautions, adverse events, dosage, and drug administration information.

8.2 Pump refill – suspected pump pocket fill

8.2.1 Remodulin pump pocket fill symptoms

During the pump refill process, it is possible that Remodulin is delivered into the subcutaneous tissue rather than the pump reservoir. Signs or symptoms of a pocket fill would likely occur within an hour of the refill procedure. A large overdose of Remodulin may result in hemodynamic collapse or death. In this event, patients may experience the following symptoms that are similar to the signs and symptoms of a Remodulin overdose.

- nausea
- vomiting
- local burning sensation
- dizziness, light-headedness
- flushing
- hypotension
- syncope
- palpitations
- dyspnea
- chest pain
- headache
- diarrhea

8.2.2 Management of a Remodulin pocket fill procedure

If you suspect a Remodulin pocket fill, perform the following actions, as necessary:

- Stabilize and medically manage the patient.
- Immediately contact a physician experienced with Remodulin, preferably the physician managing the therapy for the patient in question.
- Regularly assess the vital signs of the patient.
- Admit the patient to a monitored hospital setting, such as an intensive care unit or a step-down unit.
- Determine if the N'Vision Pump Programmer is available.
  - If the programmer is available, interrogate the pump and verify pump settings and function. Program the pump to Minimum Rate, if necessary.
  - If the programmer is not available, empty the pump reservoir to stop the drug flow (see Section 8.4).

After emergency management, re-initiate and complete the refill procedure.

8.3 Abrupt cessation or sudden large reduction of Remodulin

Abrupt cessation or sudden large reduction of therapy may result in a clinically significant or fatal drug underdose of the patient.

8.3.1 Abrupt cessation or sudden large reduction of Remodulin symptoms

The potential signs and symptoms of an abrupt cessation or a sudden large reduction of Remodulin include the signs and symptoms of returning or worsening pulmonary arterial hypertension, as well as the lack of the patient's typical Remodulin side effects. The signs and symptoms of pulmonary arterial hypertension include the following:

- dyspnea
- fatigue
- angina pectoris
- tachycardia
- pre-syncope
- syncope

The lack of the following typical side effects of Remodulin may also be characteristic of an abrupt cessation or a sudden large reduction of Remodulin:

- headache
- flushing
- diarrhea
- jaw or leg pain

8.3.2 Abrupt cessation or sudden large reduction of Remodulin procedure

If you suspect an abrupt cessation or a sudden large reduction of Remodulin, perform one or more of the following actions, as necessary:

- Medically manage the patient.
- Contact the physician managing the therapy for the patient or a physician experienced with Remodulin® (treprostinil) Injection.
- Interrogate the pump and verify the pump settings and function, see Chapter 9.
- Contact technical support or local representative and see Section A.1.2.
- Report the incident. See Section 2.4.

8.4 Emergency procedure to empty the pump reservoir

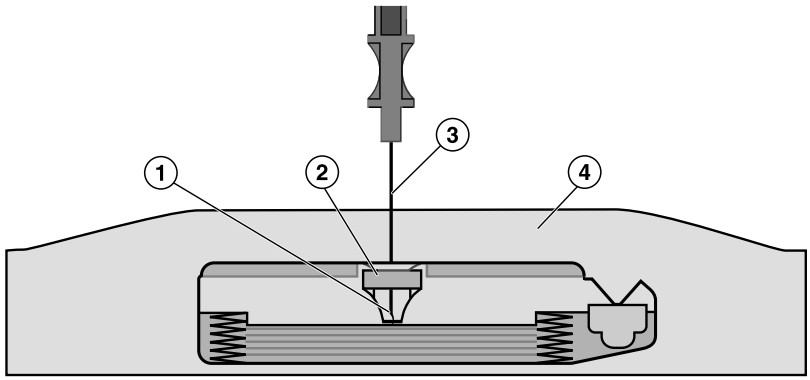
Assemble the following equipment:

- 22-gauge noncoring needle
- 20 mL syringe
- 3-way stopcock or extension set with clamp
- antiseptic agent

1. Assemble the needle, syringe, and stopcock or extension set.
2. Locate the pump by palpation. The reservoir fill port is located in the center of the pump.

   If you have difficulty identifying the pump features, you may seek assistance from another clinician. If deemed necessary by the clinician, x-ray and fluoroscopy can be used to assist in locating or determining the orientation of the pump.
3. Prepare the injection site by cleansing the area using an antiseptic agent.
4. Gently insert the 22-gauge noncoring needle into the center of the reservoir fill port until the needle touches the bottom of the reservoir fill port (see Figure 17).

Figure 17. Inside view of a pump with the needle fully and properly inserted



1 Bottom of the reservoir fill port
2 Septum
3 Needle
4 Subcutaneous tissue

During proper needle insertion, you will feel the needle:

- pass through the patient's skin and subcutaneous tissue,
- hit the silicone septum (scar tissue, if present, can feel similar to the septum),
- pass through the septum, and
- hit the metal bottom of the reservoir fill port. (The top of the pump is metal and hitting the top of the pump can feel similar to hitting the bottom of the reservoir fill port.)

  If excessive resistance is encountered during needle insertion, reassess placement. Do not force the needle. The feel of abnormal resistance during the procedure may be an indication that the needle is not in the center of the reservoir fill port.

5. Open the clamp or stopcock and slowly withdraw the fluid from the reservoir into the empty syringe.
6. Depending on pump reservoir volume, more than one syringe may be needed to empty the pump. Close the clamp or stopcock when changing syringes.
7. Completely empty the pump. When the pump is empty, the bubbles will stop forming and negative pressure in the syringe can be felt.
8. Remove the needle from the reservoir fill port.
9. Record in patient's chart the amount of fluid emptied from the pump reservoir.

9 Pump interrogation

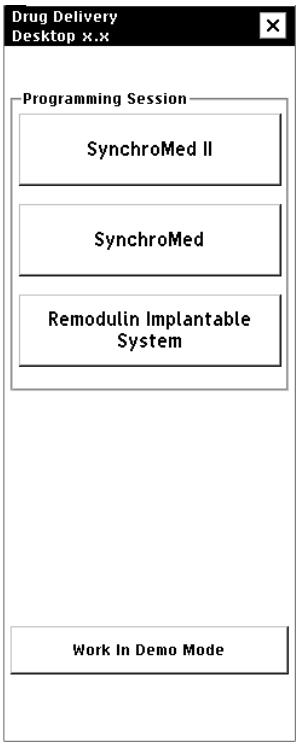
9.1 Interrogating the pump

Warning: At every patient visit, the clinician must review the Event log for any pump failures that have occurred since the last visit.

Caution: The programmer and the programming head are not sterile. To use the programmer in a sterile field, place the programming head inside a sterile sleeve before passing it into the sterile field. This action places a sterile barrier between the patient and the programming head, preventing infection. Do not sterilize any part of the programmer. Sterilization may damage the programmer or the programming head.

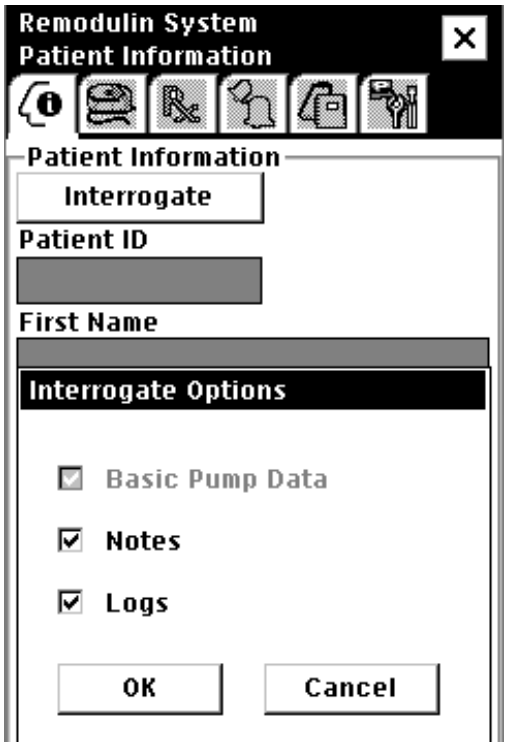
1. Turn the programmer on.
2. Select the Pump Application button from the Application Selection screen.
3. Select the Implantable System for Remodulin button from the Drug Delivery Desktop screen (see Figure 18).

Figure 18. Implantable System for Remodulin



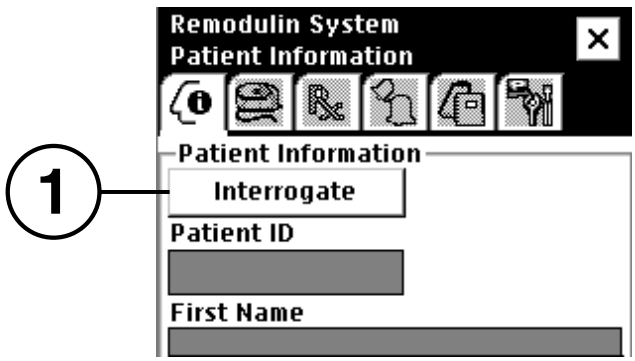
4. Retrieve all pump information by selecting the Notes and the Logs check boxes (see Figure 19).

Figure 19. Interrogate options



5. Select the Interrogate button (see Figure 20).

Figure 20. Interrogate

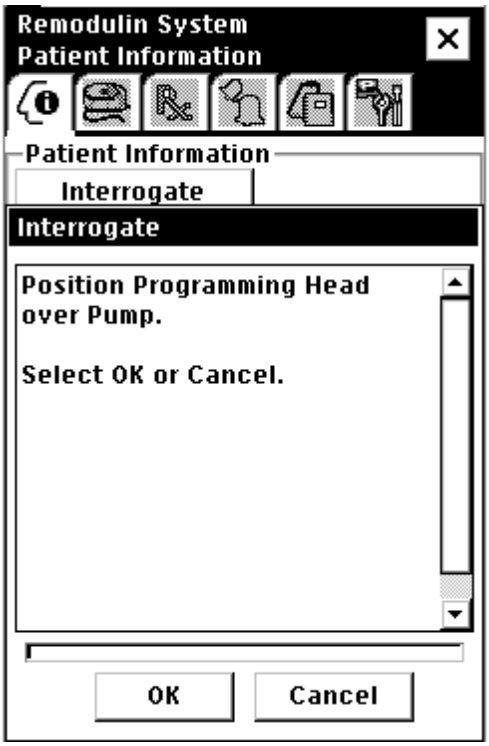


1 Interrogate button

6. Select the OK button to continue, or select the Cancel button to return to the Patient Information screen.
7. When the Interrogate dialog box appears (see Figure 21), position the programming head over the pump.

   Note: If the pump is in its shelf package, position the programming head over the target symbol on the package.

Figure 21. Interrogate dialog box

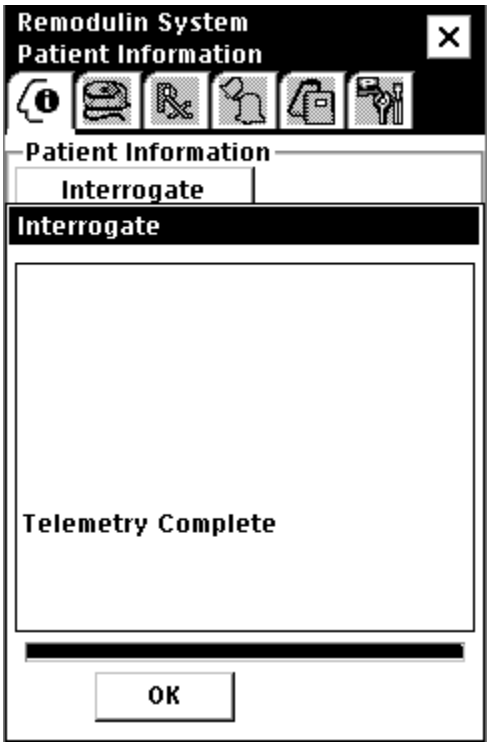


Caution: To ensure successful telemetry, hold the programming head steady over the implanted pump until confirmation is received that telemetry was successful. If the programming head is not held over the pump properly, telemetry may not be established or may be interrupted, which can result in incorrect or incomplete programming.

8. Hold the programming head steady over the pump and select the OK button.

9. When the programming head is extended, a status light is visible on the back of the programming head:
   - Green light flashing — telemetry is in progress
   - Amber light flashing — telemetry has not been established
10. Once telemetry is successfully completed and the light goes out, the Telemetry Complete message appears (see Figure 22).

Figure 22. Telemetry Complete

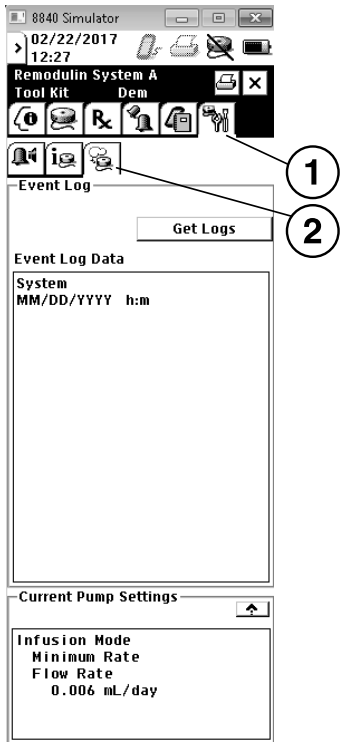


11. Select the OK button to continue. If there are any alarm events, an Attention dialog box appears.
12. If pump interrogation is successful, the Pump Status screen appears.

9.2 Reviewing the logs

1. Select the Tool Kit icon (Figure 23).

Figure 23. Get Logs



1 Tool Kit icon
2 Event Log icon

2. Select the Event Logs icon (Figure 23).
3. Scroll down through the Event Log Data.
4. Refer to Table 16 for Event Logs messages and actions for resolution.

9.3 Updating the pump

To update the pump, complete the following steps:

1. Select the Summary screen tab.

2. Select the Update Pump button and verify that the pending settings are correct.
3. Select the Yes button to accept the changes.
4. When the Update Pump dialog box appears, position the programming head over the pump.
5. Hold the programming head over the pump and select the OK button. Verifying the update can take up to a minute.
6. Select the OK button to complete the update.

10 New system implant

10.1 Preparing for system implant

1. Obtain the appropriate prescription dosage of Remodulin® (treprostinil) Injection in ng/kg/min and dosing weight in kg.

   Caution: Prior to implanting the system, confirm the appropriate location to implant the pump in the patient's body. Not selecting the correct location may result in excessive pump movement or dislodgement of the catheter from the vasculature, or may cause patient discomfort because of insufficient strain relief.

2. Consider the following when assessing if the pump size and concentration are suitable for the patient's body size:
   - Ability of patient's anatomy to accept the weight and bulk of the pump
   - Pump refill interval (see Appendix B)
   - Pump longevity (see Appendix B)
   - Time to 50% drug concentration after shutting off temporary line (see Appendix C)
3. Determine if the catheter length is suitable for the patient's body size. Consider the following:
   - Subcutaneous path length from vascular access site to pump location
   - Pump orientation and catheter wrap in the pump pocket
   - Catheter slack or redundancy in the shoulder area and pump pocket
4. Determine the amount (volume) of Remodulin for initial pump fill. Include an additional 10 mL of Remodulin to rinse the pump as part of preparing the pump for implant.
5. Before surgery, replace the existing central venous catheter with a temporary line to deliver Remodulin.

10.2 Assembling system components and supplies

Assemble the following sterile and non-sterile components and supplies:

- SynchroMed II Programmable Pump for the Implantable System for Remodulin 8637P40
- Model 8201 Implantable Intravascular Catheter
- introducer kit (8 Fr) and, if using valved introducer kit, a transvalvular introducer tool

- tunneling catheter passer
- Remodulin, 2 or 3 vials
- sterile saline
- 20 mL syringes (2)
- 3 mL syringes (2)
- 20- to 22-gauge needles (2)
- sterile sleeve
- extension set with clamp
- 0.22 micron filter
- N'Vision Model 8840 Clinician Programmer with the 8870 Application Card

10.3 Preparing the catheter for implant

Warnings:

- Do not force the catheter through the vasculature if significant resistance is encountered during passage of the catheter. Applying force may injure the patient's vasculature or heart.
- Do not use Remodulin to flush the catheter. Doing so will result in high concentrations of Remodulin being delivered during the priming bolus, which may lead to a clinically significant or fatal overdose of Remodulin.

Cautions:

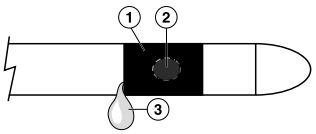
- Handle the catheter with care at all times. Do not use the catheter if it has been damaged. A damaged catheter may allow blood to enter the catheter valve and occlude the catheter, resulting in a reduced or an abrupt cessation of drug delivery.
- Before implanting the catheter, determine if the catheter length is suitable for the patient's body size. A catheter that is too short may result in dislodgement of the catheter from the vasculature or may cause patient discomfort because of insufficient strain relief. A catheter that is too long may result in difficulty wrapping the excess length and securing it under the pump. Do not cut the catheter to size for the patient.
- When preparing the catheter for implant, do not connect the sutureless connector to the catheter until instructed to do so.
- Do not use a needle to flush the catheter. The needle may puncture the catheter, allowing drug to leak into the surrounding tissue when the catheter is implanted. Leakage may result in a site reaction or a drug underdose.
- Do not wipe the distal tip of the catheter with gauze or with your fingertips. Damage may occur. Do not touch or contact the one-way valve. Doing so may cause an inversion of the one-way valve, which may lead to a catheter occlusion and an abrupt cessation of drug delivery.
- If the catheter cannot be successfully flushed, select a new catheter and repeat the steps in this section. An occluded catheter may result in a loss of or a change in therapy, which may lead to a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug underdose.

Flush the catheter with sterile saline solution before implanting the system. To flush the catheter, perform the following steps:

Caution: Slowly inject the sterile saline solution into the catheter. Injecting the sterile saline solution too quickly or with too much force can damage the catheter. A damaged catheter may allow blood to enter the catheter valve and occlude the catheter, resulting in a reduced or an abrupt cessation of drug delivery.

1. Flush the catheter with a 3 mL syringe filled with sterile saline solution. Apply light pressure to the syringe plunger until the sterile saline solution drips from the sleeve valve.
2. Visually observe that the sterile saline solution drips from the sleeve valve (see Figure 24).

Figure 24. Sleeve valve covering the side hole of the catheter



1 Sleeve valve
2 Side hole
3 Sterile saline solution dripping from the sleeve valve

3. Visually examine the distal tip of the catheter for damage. Verify that the sleeve valve is intact and that it covers the side hole.

10.4 Preparing the pump

Implanting physicians should be experienced in pump and catheter implant procedures and should be thoroughly familiar with all product labeling. Preparing the pump for implant involves establishing telemetry between the programmer and the pump. For general information on establishing telemetry between the programmer and the pump, to obtain pump status information, and to begin a new programming session, see Section 9.1.

Warning: Before the patient receives a new system implant, Remodulin must be delivered to the patient through an external line. Failure to deliver Remodulin through an external line can lead to a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal overdose of Remodulin. All procedures where an external line is used to provide supplemental therapy require that the implanted pump be first reprogrammed to the Minimum Rate for infusion before beginning supplemental therapy. Failure to do so may result in a clinically significant drug overdose including hemodynamic collapse or death.

Cautions:

- Do not implant a pump that has been dropped onto a hard surface or shows signs of damage. Implanting a pump that has been dropped or damaged can result in unintended therapy, including a potential drug overdose or underdose of the patient, and requires additional surgery to replace the pump.
- Do not implant the pump unless pump operation has been confirmed. Failure to confirm pump operation before implant can result in additional surgery to replace the pump.
- Do not prematurely activate the pump reservoir valve by overpressurizing the reservoir. Activation of the pump reservoir valve seals the pump reservoir closed. Unusual resistance or the inability to inject the entire fill volume may indicate activation of the pump reservoir valve. If the valve closes, a portion of the reservoir contents must be delivered or removed before completing filling the pump. Procedural delays can occur. To prevent activation of the pump reservoir valve during emptying and filling procedures, take the following actions:
  - Completely aspirate all contents of the pump reservoir before filling.
  - Do not allow air into the pump reservoir through an open needle in the septum or an unclamped extension.
  - Do not exceed the maximum reservoir volume indicated in the pump labeling.
- The programmer and the programming head are not sterile. To use the programmer in a sterile field, place the programming head inside a sterile sleeve before passing it into the sterile field. This action places a sterile barrier between the patient and the programming head, preventing infection. Do not sterilize any part of the programmer. Sterilization may damage the programmer or the programming head.
- Install and use the filter at the indicated steps. The filter prevents air in the syringe or tubing from entering the pump reservoir and filters foreign material, including bacteria, from entering the reservoir. Air in the reservoir may prevent the pump from properly filling and may cause activation of the pump reservoir valve seal before the pump is completely filled with drug. Unfiltered foreign material or bacteria may result in contaminated drug and may lead to a systemic infection.
- Monitor the patient for symptoms of overdose, underdose or worsening symptoms. Infusion variability between the old pump and the new pump may be observed as a change in patient symptoms related to either overdosing or underdosing and may require an adjustment in dosing.

10.4.1 Prepare to empty the pump

Warning: The calibration constant displayed on the programmer screen after reading the pump status must match the calibration constant printed on the shelf package. If calibration constants differ, contact the appropriate representative listed in Section 2.4. Using an incorrect calibration constant may result in a clinically significant or fatal drug underdose or overdose of the patient.

1. Before opening the shelf package, position the programming head over the target symbol on the bottom of the pump package. Use the programmer to interrogate the pump and confirm the following from the Pump Status screen:
   - pump battery status
   - current pump settings
   - no active alarm events. If the pump is still in Shelf State, audible alarms are disabled. The pump must be interrogated to determine if an alarm has been activated.
   - pump calibration constant (Cal. Constant) displayed on the screen matches the calibration constant printed on the shelf package
2. Select the OK button to close the Pump Status screen.
3. Open the pump shelf box. Remove the FOR YOUR RECORDS label from the pump shelf box and attach the label to the patient's record. This label displays the pump model number, the reservoir size, the calibration constant, and the serial number.

10.4.2 Sterile procedure

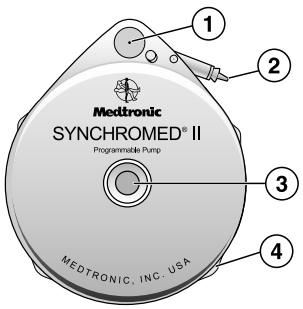
1. Once a sterile table is available and the sterile field is established, pass the sterile pump package and sterile accessories into the sterile field.
2. Open the sterile pump package and remove the pump.
3. Remove the protective cap from the catheter port. (A small amount of water may be present in the protective cap.)

10.4.3 Empty the pump

Caution: Ensure tubing is clamped at the steps where indicated to prevent introduction of air into the pump reservoir and to prevent water or drug from returning to the pump. Air in the reservoir may prevent the intended amount of drug from being dispensed into the reservoir and may cause the reservoir valve to activate before the pump is completely filled with drug.

1. Assemble the 22-gauge, noncoring needle (black sheath) from the pump package to the extension tubing with clamp.
2. Attach an empty 20 mL syringe to the extension tubing with clamp.
3. Close the clamp.
4. Insert the needle into the reservoir fill port until the needle touches the metal needle stop (see Figure 25).

Figure 25. Pump exterior view



1 Catheter access port	3 Reservoir fill port
2 Catheter port on the pump	4 Suture loop

5. Open the clamp on the extension tubing.
6. Withdraw the sterile water from the pump into the empty syringe (the pump is shipped nearly full).
7. If the volume of fluid in the pump reservoir exceeds the volume of the syringe used for emptying, close the clamp on the extension tubing and remove the filled syringe. Attach an empty syringe, open the clamp on the extension tubing, and repeat until the pump reservoir is empty.
8. Empty the pump reservoir until air bubbles no longer appear in the syringe, ensuring that all water and air are removed from the pump reservoir.
9. If another syringe is required, repeat the process with an additional syringe.
10. Close the clamp on the extension tubing and remove the syringe from the extension tubing.

10.4.4 Rinse the pump reservoir

Caution: If the water in the pump reservoir is not emptied or the rinse is not performed, the water will mix with the drug when the pump is filled and will dilute the drug in the pump reservoir. As a result the patient will not receive the intended dosage and may experience symptoms of underdosing.

It is recommended that you rinse the pump reservoir twice with 5 mL of Remodulin each time.

Notes:

- The pump reservoir capacity is 40 mL. Because some sterile water remains in the pump reservoir, the final concentration of drug varies based on the fill method (see Table 9).
- The expected concentration of Remodulin in the pump reservoir is based on the assumption that the reservoir is filled to capacity at implant.

Table 9. Expected concentration of drug in the pump reservoir based on fill method

Pump reservoir capacity	Filling without rinsing	Rinsing with 5 mL of drug (x2)
8637P-40	97%	100%

1. Fill a syringe with 5 mL of Remodulin, using the same concentration of Remodulin as intended for the therapy.
2. Attach the filter to the Remodulin-filled syringe and prime the filter.
3. Attach the syringe with filter to the extension tubing and noncoring needle in the reservoir fill port.
4. Open the extension tubing clamp. Slowly inject 5 mL of Remodulin into the reservoir. Close the extension tubing clamp.
5. Remove the syringe with filter from the extension tubing.
6. Attach an empty 20 mL syringe to the extension tubing.
7. Open the extension tubing clamp. Withdraw fluid from the pump reservoir until air bubbles stop flowing into the extension tubing and syringe and negative pressure is felt. Close the extension tubing clamp.
8. Remove the syringe from the extension tubing.
9. Discard the liquid in the syringe.
10. Repeat Step 1 through Step 9 until the 2 rinse cycles are completed.

10.4.5 Fill the pump

Caution: Do not fill the pump with Remodulin above its labeled capacity. If the pump is overfilled with Remodulin, the actual flow rate exceeds the programmed flow rate and the patient may be overdosed.

1. Fill a syringe or syringes with slightly more than the desired amount of Remodulin.

   Note: Fill the syringe with Remodulin slowly to minimize foaming and air bubbles in the syringe.

2. Attach the filter to the Remodulin-filled syringe and prime the filter.
3. After priming the filter, discard excess Remodulin so the syringe contains the desired amount and does not exceed the capacity of the pump.

   Caution: Ensure that the recorded volume is the actual volume in the syringe after priming the filter. A discrepancy between the volume recorded and the volume dispensed into the pump may lead to an underdose or an abrupt cessation of therapy for the patient.

4. Record the actual fill volume of the syringe.
5. Attach the Remodulin-filled syringe with filter to the extension tubing and noncoring needle in the reservoir fill port.
6. Open the extension tubing clamp.
7. Slowly inject Remodulin into the reservoir.
8. Close the extension tubing clamp.
9. When filling is complete, remove the needle from the pump reservoir fill port.

   Note: If the reservoir valve is activated before the pump is completely filled, follow the steps in Section A.8 to empty the reservoir.

10.4.6 Flush the catheter access port with sterile saline

Warning: Do not use Remodulin to flush the catheter access port. Doing so will result in Remodulin being delivered during the priming bolus, which may lead to a clinically significant or fatal overdose of Remodulin.

1. Fill a 3 mL syringe with 1 to 2 mL of sterile saline solution.
2. Attach the 24-gauge, noncoring needle (purple sheath) included in the pump package to the syringe.

3. Gently insert the needle into the catheter access port until the needle touches the metal needle stop.
4. Inject all of the sterile saline into the catheter access port.
5. Remove the needle from the catheter access port and save for use during the system integrity check.

10.4.7 Remove Remodulin from the exterior of the pump

Warning: Before the pump is implanted in the patient, wipe the exterior of the pump with gauze to remove any Remodulin. Remodulin on the exterior of the implanted pump could cause a local tissue reaction or an overdose of the patient.

1. Use gauze to wipe the exterior of the pump.
2. Confirm that no Remodulin is left on the exterior of the pump.

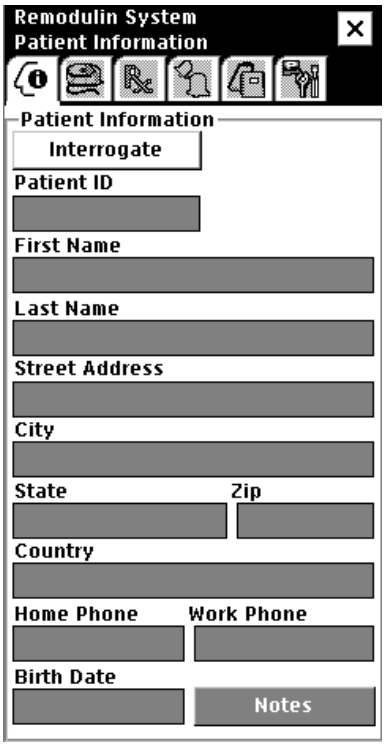
10.5 Programming on the back table

10.5.1 Enter patient information

1. Pass the programming head into the sterile field with the programming head inside a sterile sleeve. If the programmer was shut off, turn the programmer back on and re-interrogate the pump.
2. Enter patient information:
   a. Select the Patient Information screen tab.

   b. Select the appropriate input boxes, and enter patient name, ID number, and any other appropriate patient information (see Figure 26).

Figure 26. Patient Information boxes



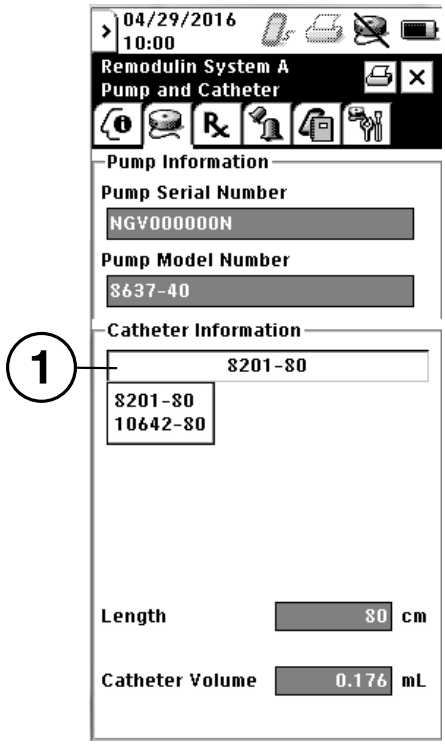
10.5.2 Enter pump and catheter information

Warning: Confirm the intended catheter is selected and programmed. Selecting and programming an incorrect catheter model number may lead to a potential drug overdose or underdose of the patient.

1. Select the Pump and Catheter screen tab.

2. Select the Catheter Information button and select the appropriate catheter from the drop-down list (see Figure 27).

Figure 27. Catheter Information



1 Field showing catheter selected

Once the appropriate catheter is selected, the Length and Catheter Volume fields automatically populate with the correct values.

10.5.3 Enter Remodulin information

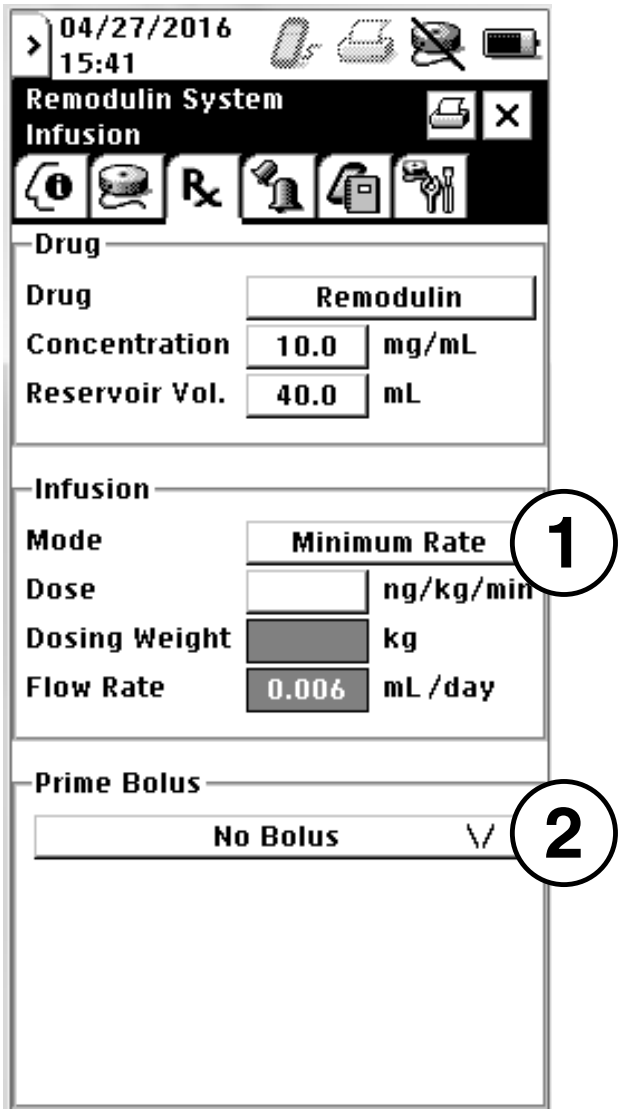
Warning: Do not program a prime bolus on the back table for a new system implant. Doing so may result in Remodulin being delivered during the system integrity check, which may lead to a clinically significant or fatal dose of Remodulin.

Warning: Confirm that the intended Remodulin concentration is selected and programmed. Selecting and programming an incorrect Remodulin concentration may lead to a potential drug overdose or underdose of the patient.

1. Select the Infusion screen tab.

2. Select the Drug button and select Remodulin from the drop-down list.
3. Select the Concentration button and select the appropriate concentration from the drop-down list.
4. Select the Reservoir Vol. button and enter the volume of Remodulin that is currently in the pump.
5. Select the OK button to continue. The reservoir volume is displayed on the Reservoir Vol. button.
6. Verify that the Infusion Mode is at Minimum Rate and that the Prime Bolus has No Bolus selected (see Figure 28).

Figure 28. Infusion Mode and Prime Bolus



1 Minimum Rate selected as Mode
2 No Bolus selected under Prime Bolus

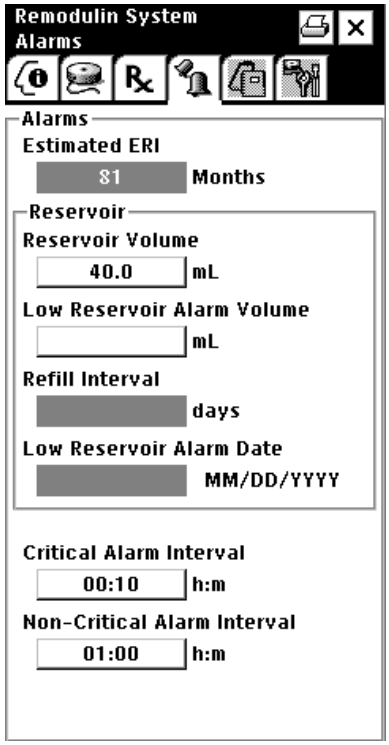
10.5.4 Set the Low Reservoir Alarm Volume

Warning: Adjusting the Low Reservoir Alarm Volume lower than recommended may result in an abrupt cessation of therapy if the pump empties before the alarm is set to sound.

1. Select the Alarms screen tab.

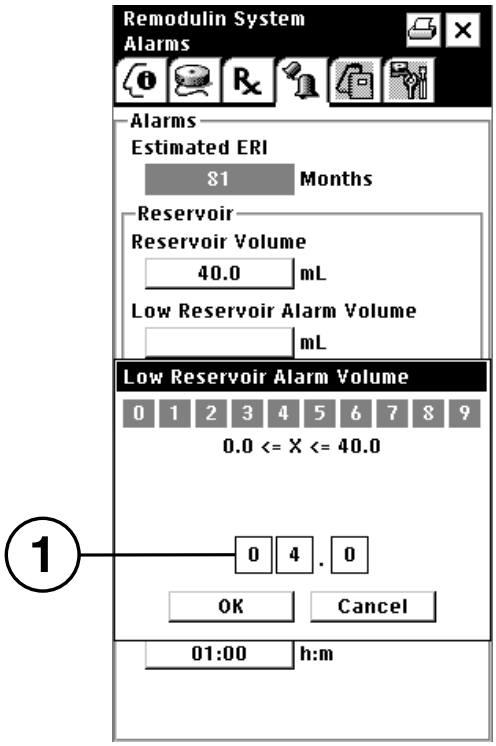
2. Select the Low Reservoir Alarm Volume button (see Figure 29).

Figure 29. Low Reservoir Alarm Volume



3. Confirm that the Low Reservoir Alarm Volume is set to 4.0 (see Figure 30).

Figure 30. Low Reservoir Alarm Volume set to 4.0



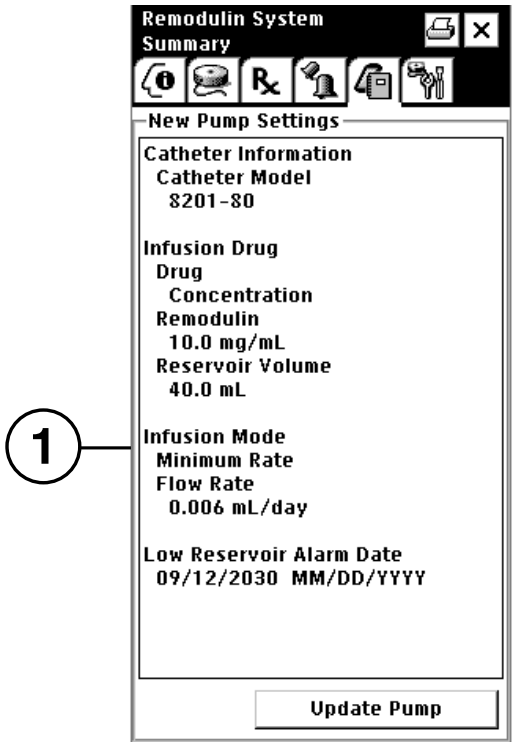
1 4.0 selected as the Low Reservoir Alarm Volume

4. Select the OK button to accept the value.

10.5.5 Update the pump

1. Update the pump (see Section 9.3).
2. On the New Pump Settings screen, verify that the Infusion Mode is set to Minimum Rate (see Figure 31).

Figure 31. New Pump Settings



1 Minimum Rate selected as the Infusion Mode

3. Also verify that the values for the catheter and the infusion are correct.

10.6 Implanting the catheter

10.6.1 Select an introducer delivery system

Cautions:

- Use an 8 Fr introducer without a retained guide wire. Use of an introducer with a retained guide wire can damage the catheter.
- If a valved introducer is used, a 9 Fr transvalvular introducer tool must be used to prevent damage to the catheter.

Use a compatible introducer delivery system to implant the catheter. A compatible introducer delivery system includes an 8 Fr introducer that is peelable, splittable, or slittable. The 8 Fr introducer may or may not include a hemostasis valve.

10.6.2 Gain venous access

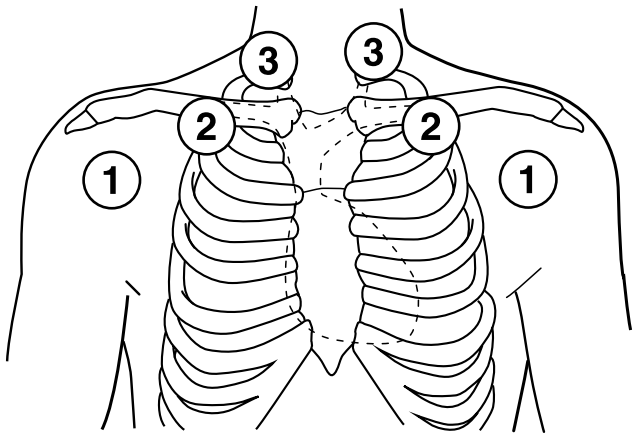
Cautions:

- When using a subclavian approach for catheter insertion, use a more lateral approach to minimize the risk of first rib clavicular crush. First rib clavicular crush may subsequently fracture the body of the catheter.
- Certain anatomical abnormalities, such as thoracic outlet syndrome, may pinch and subsequently fracture the catheter.

Select a venous insertion site for the catheter based on the planned vascular path. See Figure 32 for the suggested insertion sites.

Note: The cephalic cutdown method is recommended to minimize risk of pneumothorax.

Figure 32. Suggested insertion sites for the catheter



1 Cephalic cutdown
2 Subclavian or axillary stick
3 Jugular

10.6.3 Insert the catheter into the vein

Warning: Do not force the catheter through the vasculature if significant resistance is encountered during passage of the catheter. Applying excessive force may injure the patient's vasculature or heart, or the catheter.

Use caution when inserting the catheter into the vein:

- Do not severely bend, kink, or stretch the catheter.
- Do not use surgical instruments to grasp any part of the catheter.
- Do not insert any tool into the lumen of the catheter, such as a wire or a stylet.

Insert the catheter through the introducer into the vein.

To insert the catheter into the vein, perform the following steps:

1. Insert a compatible introducer into the vein.

   Note: Use the vein pick, as necessary, to gain access to the chosen vein.

2. Advance the catheter via the introducer into the superior vena cava (SVC). See the introducer product literature for additional information on the use of the introducer.
3. Advance the catheter through the vasculature into the SVC.

   Note: If venous tortuosity prevents advancement of the catheter tip into the SVC, a longer or kink-resistant introducer may be used.

4. Remove the introducer from the catheter and vasculature.

10.6.4 Avoid damage to the sleeve valve or distal tip of the catheter

Use caution to avoid damage to the distal tip of the catheter after it is inserted through the introducer.

Caution: The catheter sleeve valve may be damaged if the catheter tip is pulled back through the introducer.

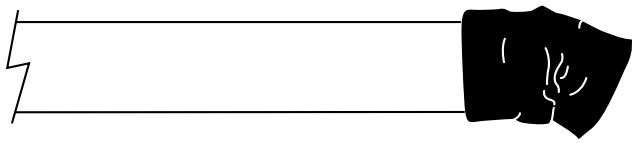
If the catheter must be pulled back through the introducer, slowly pull the catheter completely out of the introducer and then inspect the catheter sleeve valve for damage. Damage can include, but is not limited to, a torn catheter sleeve valve or an inverted catheter sleeve valve.

See Figure 33 for an example of a torn catheter sleeve valve.

Figure 33. Torn catheter sleeve valve

See Figure 34 for an example of an inverted catheter sleeve valve.

Figure 34. Inverted sleeve valve



10.6.5 Position the tip of the catheter

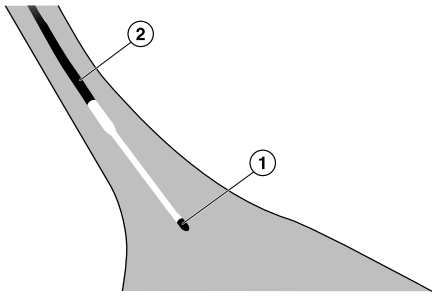
When positioning the tip of the catheter during implant, use caution to ensure that the catheter tip is not wedged against the vasculature or the heart wall. Allow the tip to free-float in the superior vena cava (SVC).

Warning: Do not advance the catheter into the right atrium or atrial fibrillation may occur.

To position the tip of the catheter, perform the following steps:

1. Advance the distal tip of the catheter to the SVC-atrial confluence just outside the right atrium.
2. Position the anchoring sleeve at the venous access site.
3. Use fluoroscopy to verify the location of the distal tip of the catheter at the SVC-atrial confluence (see Figure 35). Verify that the distal tip is not in contact with the vessel wall.

Figure 35. Implanted catheter under fluoroscopy



1 Distal tip of the catheter under fluoroscopy
2 Catheter body under fluoroscopy

Note: The distal tip of the catheter has an enhanced radiopaque marker band to aid in catheter tip placement under fluoroscopy.

10.6.6 Anchor the catheter

Caution: Verify that the catheter is anchored properly. Improper or incomplete anchoring may result in catheter dislodgement from the vasculature or catheter occlusion.

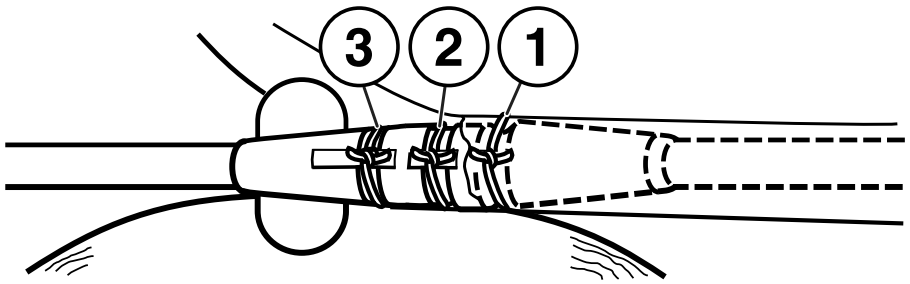
The anchoring sleeve is used to secure the catheter to muscle or fascia with sutures. When securing the anchoring sleeve:

- Do not tie a suture directly onto the catheter body. Tie the sutures to the anchoring sleeve.
- Do not attempt to remove or alter the anchoring sleeve.
- Do not move the catheter while suturing.
- Do not use absorbable suture ties.
- Do not occlude the catheter lumen by tying the sutures too tightly.
- Do not use the anchoring sleeve tabs for suturing.

To anchor the catheter, perform the following steps:

1. Secure suture groove 1 of the anchoring sleeve to the vein, if needed for hemostasis, with a non-absorbable suture (see Figure 36).
2. Secure the anchoring sleeve to the catheter with 2 suture ligatures tied tightly enough to slightly indent the catheter coils. Use the second and third grooves to secure anchoring sleeve to the catheter body only (see Figure 36). Do not secure the anchoring sleeve to tissue.

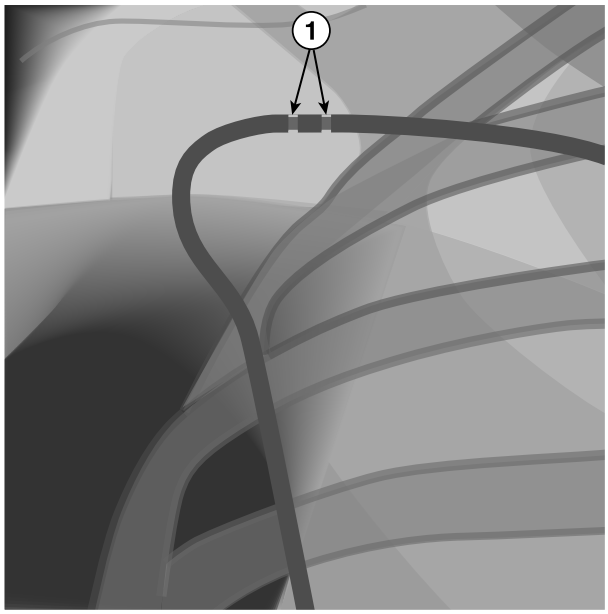
Figure 36. Secure the anchoring sleeve to the vein and the catheter body



1 Suture secured around the vein
2 Suture secured to the anchoring sleeve only
3 Suture secured to the anchoring sleeve only

3. Use fluoroscopy to verify that the coil beneath the sutures is indented. If the coil is not indented, tie the anchoring sleeve again. Visual indents ensure that the compressive force is adequate. The indents appear as reduced radiopacity of the catheter body (see Figure 37).

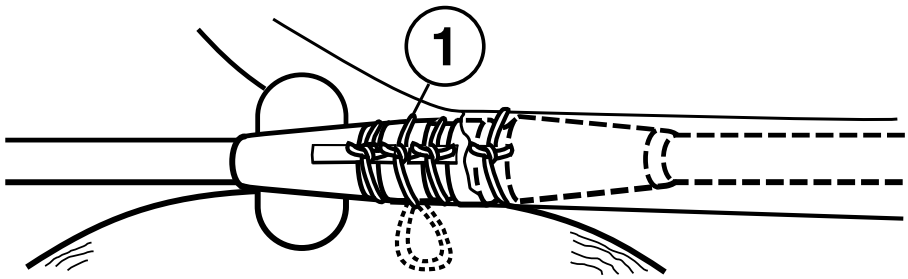
Figure 37. Verify that the coil beneath the sutures is indented[2]



1 Two indents on the catheter body

4. Secure the anchoring sleeve to fascia with one or more sutures tied through tissue and around the anchoring sleeve (see Figure 38).

Figure 38. Securing the anchoring sleeve to fascia



1 Suture tied around the anchoring sleeve and secured to fascia or tissue

[2] Do not rely on the fluoroscopy image for determination of adequate sutures. The fluoroscopy image has not been validated.

5. Use the retention sleeve if additional sutures are needed for the catheter.
6. Verify under fluoroscopy that the catheter tip is still positioned as intended.

10.7 Preparing the pump pocket

Prepare the subcutaneous pocket using an incision in the lower abdomen.

Ensure that the subcutaneous pump pocket allows the pump to be implanted within 2.5 cm from the surface of the skin and in an area where sutures will not be directly over the reservoir fill port or catheter access port.

Select a location between the rib and iliac crest that is:

- Away from bony structures (3 to 4 cm) to minimize discomfort at the pump site
- Away from areas of restriction or pressure to minimize the potential for skin erosion and patient discomfort
- Away from existing scar tissue
- A minimum of 20 cm away from another programmable device to minimize telemetry interference and incorrect or incomplete programming
- Appropriate for healing for patients with scleroderma. Avoid locations where skin or soft tissue may heal poorly or have increased susceptibility to infection

10.8 Tunneling the catheter

Prior to tunneling the catheter, select a compatible tunneling tool that allows passage of a catheter, including the catheter connection (see Section 3.4.3 for the catheter dimensions). Refer to the applicable instructions for use for the tunneling tool.

Caution: Use caution when performing the tunneling procedure to prevent the tunneling tool from perforating the diaphragm or internal organs.

To tunnel the catheter, perform the following steps:

1. Tunnel subcutaneously between the venous access site and the pump pocket site with a tunneling catheter passer.

   Note: If you tunnel starting at the venous access site to the pump pocket, use a tunneling tool with a removable handle. Remove the obturator from the tunneling tool handle after tunneling is completed. Remove the tunneling tool handle from the tunneling tool.

2. Insert the catheter directly into the open lumen of the tunneling tool shaft.

   Caution: Use caution when passing the catheter to the pump pocket site. The catheter can be dislodged or damaged if it is handled roughly.

3. Pass the catheter from the venous access site to the pump pocket site.
4. Hold the catheter at the venous access site while removing the tunneling tool. Slowly remove the tunneling tool from the tunneling path through the abdominal pocket site.
5. Adjust the catheter slack between the venous access site and the pump pocket site. Ensure that sufficient catheter slack is present at the venous access site.

10.9 Implanting the pump

10.9.1 Attach the catheter to the sutureless connector

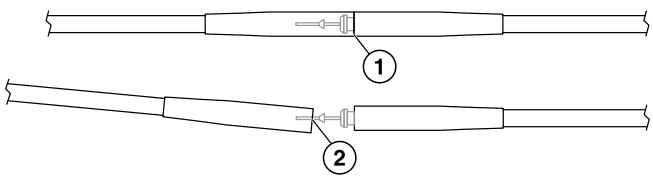
Warning: Verify that the sutureless connector is secured correctly to the catheter. Failure to connect the sutureless connector securely to the catheter may allow Remodulin to leak from the junction. If Remodulin leaks from the junction, a localized site reaction may occur. If Remodulin is not delivered in the prescribed amount, the patient may be underdosed.

To attach the catheter to the sutureless connector, perform the following steps:

1. Align the sutureless connector pin with the lumen of the catheter.
2. Insert the sutureless connector pin straight into the lumen of the catheter.
3. Ensure that there is no gap between the connection of the proximal end of the catheter connector and the sutureless connector.

   Figure 39 shows the sutureless connector inserted correctly and incorrectly into the catheter connector.

   Figure 39. Sutureless connector pin inserted correctly and incorrectly into the lumen of the catheter

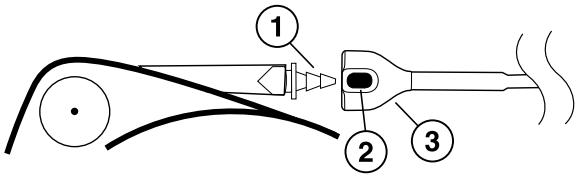


1 Sutureless connector pin inserted correctly into the lumen of the catheter
2 Sutureless connector pin inserted incorrectly into the lumen of the catheter

10.9.2 Attach the sutureless connector to the pump

1. Connect the sutureless connector to the pump by pinching the black oval dots on the proximal end of the sutureless connector (see Figure 40).

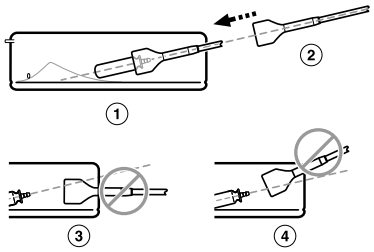
Figure 40. Connecting the sutureless connector to the pump



1 Catheter port on the pump
2 Oval on the sutureless connector
3 Tapered portion of the sutureless connector

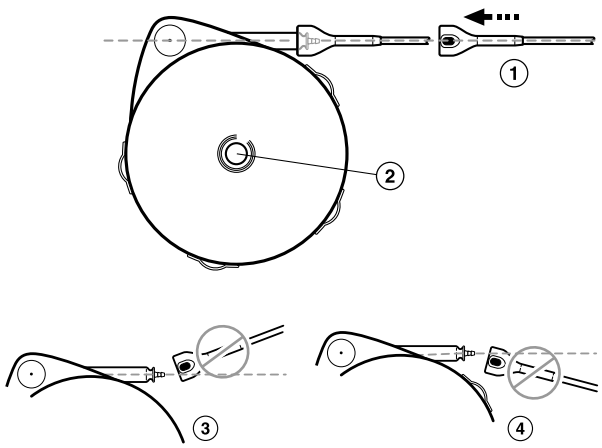
2. Examine Figure 41 and Figure 42. These figures depict correct alignment and incorrect alignment of the sutureless connector to the pump.

Figure 41. Connector — correct and incorrect alignment



1 Catheter port on this side
2 Correct alignment
3 Incorrect alignment
4 Incorrect alignment

Figure 42. Pump view — correct and incorrect alignment



1 Correct alignment
2 Reservoir fill port
3 Incorrect alignment
4 Incorrect alignment

3. Check for proper connection by gently tugging (Figure 43) and freely rotating (Figure 44) the sutureless connector on the pump.

Figure 43. Tug to check for proper connection

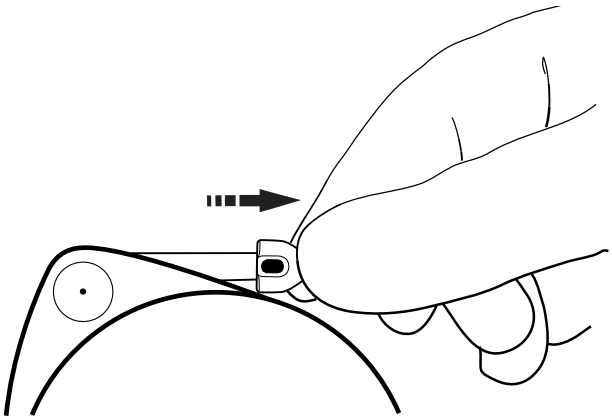
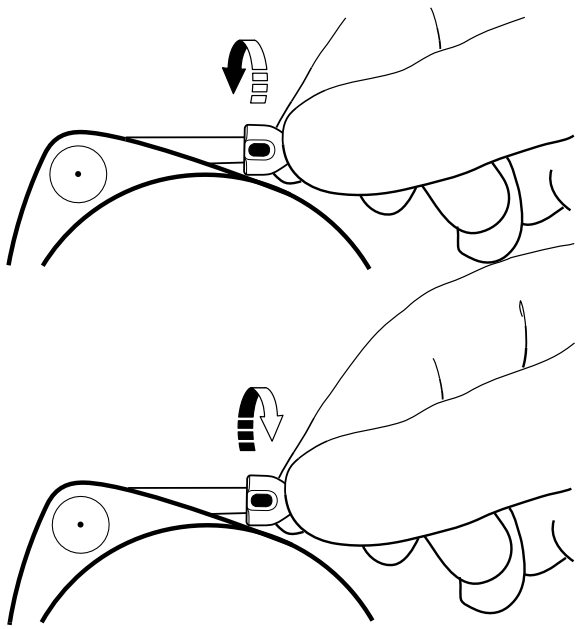


Figure 44. Rotate to check for proper connection



10.9.3 Check system integrity

Warning: Verify that the sutureless connector is secured correctly to the catheter and the pump. Failure to connect the sutureless connector securely to the catheter and the pump may allow Remodulin to leak from the junction. If Remodulin leaks from the junction, a localized site reaction may occur. If Remodulin is not delivered in the prescribed amount, the patient may be underdosed.

Warning: Do not use Remodulin to flush the system during the system integrity check. Doing so will result in Remodulin being delivered during the priming bolus, which may lead to a clinically significant or fatal overdose of Remodulin.

Caution: The following flush may bolus any drug residing in the fluid path. Consider the location of the drug in the fluid path before flushing.

Perform a system integrity check. This check verifies that there are no leaks or occlusions at any of the connections.

1. Obtain a new 20- to 22-gauge needle and attach the needle to a new 3 mL syringe.
2. Fill the syringe with sterile saline.
3. Replace the 20- to 22-gauge needle on the syringe with the 24-gauge, noncoring needle (purple sheath) that was used in preparing the pump for implant. Do not use a filter on the syringe.
4. Gently insert the needle into the catheter access port until the needle touches the metal needle stop.

   Caution: Failure to slowly inject the saline may damage the sleeve valve of the catheter, requiring catheter replacement.

5. Slowly inject the saline into the catheter access port at an approximate rate of 0.1 mL/s. Verify that there is no saline leaking from any connection junctions and that there is low resistance and easy fluid flow while injecting the saline.
6. Remove the needle from the catheter access port.

10.9.4 Implant the pump

Cautions:

- Implant the pump no more than 2.5 cm from the surface of the skin to maintain access to the reservoir and catheter access ports.
- Place the pump in the prepared pocket so that the reservoir fill port is anteriorly oriented and the reservoir fill port and the catheter access port are easy to access after implant.
- Place the pump so that no sutures to the skin are directly over the reservoir fill port or the catheter access port.

Improper component placement can result in inaccessible pump ports, inadequate drug delivery, component damage, or procedural delays, and may require surgical revision or replacement.

1. Place the filled pump into the prepared pocket.

   Cautions:

   - Secure the catheter body well away from the pump ports.
   - Place the sutureless connector on the outside of the pump perimeter with the excess catheter body wrapped underneath the pump. Do not kink or twist the excess catheter body.
   - Place the sutureless connector outside of the pump's suture loops before suturing the pump.

2. Place the excess catheter body into the pump pocket:
    a. Ensure that the sutureless connector and its connection are wrapped outside of the pump perimeter away from the pump's suture anchor sites, and that the sutureless connector is still visible under fluoroscopy.
    b. Wrap any excess catheter body behind the pump.
3. Suture the pump in the subcutaneous pocket using the following steps:
    a. Suture the first 2 suture loops to the fascia in the bottom of the subcutaneous pocket.
    b. Use these 2 sutures and the lower suture loops on the pump to draw the pump into the pocket.
    c. Tie the sutures.
    d. Suture the remaining 2 loops at the top of the pump pocket.
    e. Tie the sutures, securing the pump into the pocket.
4. Irrigate the pump pocket.
5. Close the incisions per normal procedure and apply dressing.

10.9.5 Programming procedures after implanting the pump

See Chapter 11 for prime programming procedures and transitioning Remodulin delivery to the implanted system.

11 Programming after new system implant

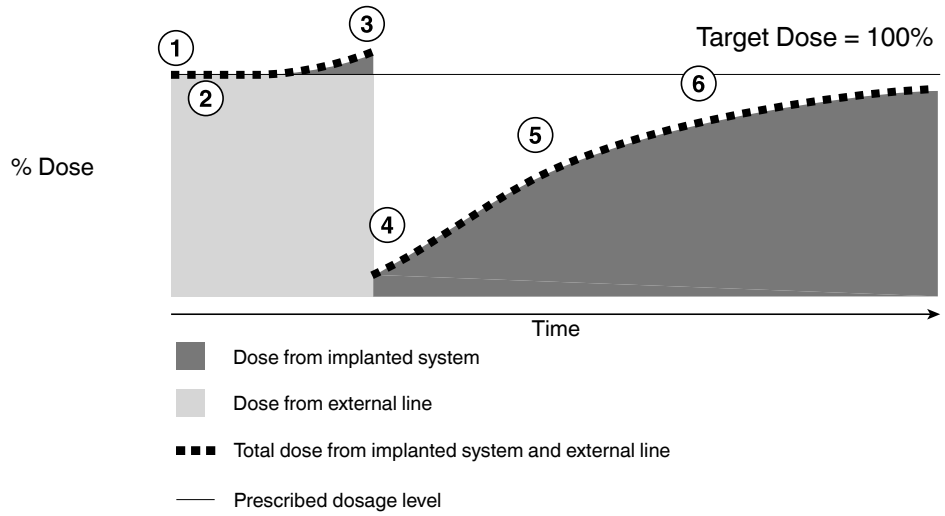
11.1 Prime for New System Implant overview

Prime for New System Implant is performed following a new system implant. The pump reservoir is filled with Remodulin® (treprostinil) Injection, the pump tubing is filled with water, and the catheter is filled with saline. Before you perform the Prime for New System Implant, verify that Remodulin is being delivered through an external line.

The typical dosing profile for Prime for New System Implant, including the dose delivered by the external line, is shown in Figure 45.

Note: The actual time to events 3, 5, and 6 is dependent on the patient's dose. See the programmer for the actual times for your patient.

Figure 45. Typical dosing profile for Prime for New System Implant



1 Prime Bolus start = 100% dose from external line + 0% dose from implanted system
2 Prime Bolus end = 100% dose from external line + 0% dose from implanted system
3 Before external line turned off = 100% dose from external line + 20% dose from implanted system
4 External line turned off = 0% dose from external line + 20% dose from implanted system
5 Implanted drug delivery continues = 0% dose from external line + 50% dose from implanted system
6 Implanted drug delivery continues = 0% dose from external line + 80% dose from implanted system

Before you perform the Prime for New System Implant (prime), Remodulin is already being delivered through an external line. As the prime begins, the drug mixes with water and saline in the pump tubing and the catheter. A minimal amount of Remodulin (<0.1 mg) exits the catheter tip during the prime.

After the prime ends, the pump switches to the therapeutic rate (simple continuous rate). Diluted Remodulin begins to exit the catheter tip and is delivered to the patient through the implanted system. After the prime, the concentration of Remodulin at the catheter tip increases slowly. The programmer calculates the time duration to turn off the external line, which is the time that the implanted system takes to reach 20% dose (nominal) for the average patient.

11.2 Programming the pump

11.2.1 Initial steps

Warning: Conduct the Prime for New System Implant procedure under the supervision of a PAH clinician. An overdose or an underdose of the patient may occur and may require medical management of the patient.

Warning: Mixing of drug and non-drug (sterile water, saline) fluids occurs at the high flow rate used during a priming bolus. This mixing can result in a period of reduced drug concentration following the priming bolus. This mixing can lead to adverse events involving drug overdose prior to turning off the external line or drug underdose after the external line has been turned off. Follow these guidelines regarding priming bolus and the transition from the external line to the implanted system :

- Perform the Prime for New System Implant procedure under the supervision of a PAH clinician. Closely monitor the patient during the transition of Remodulin delivery from the external line to the implanted system. An overdose or underdose of the patient may occur during this transition and may require medical management of the patient. In the DellVery for PAH clinical study, all patients were monitored overnight in a hospital setting.
- If signs of an overdose (identified in Section 8.1.1) occur before the external line is turned off, the external line may be turned off earlier than the calculated time provided by the programmer.
- Based on the therapeutic index of Remodulin and the sensitivity of the patient, some individuals may need additional monitoring until the delivered drug reaches the intended concentration. If signs of an underdose (identified in Section 8.3.1) occur, do not increase the programmed daily dose within the first 72 hours following a priming bolus as the delivered drug may not have reached the intended concentration during this time.

- Educate caregivers and family members to recognize the signs and symptoms associated with Remodulin underdose and withdrawal. Instruct them to contact the patient's physician if they notice any of these signs or symptoms and to seek emergency assistance as necessary.

Program the Prime for New System Implant to advance the drug from the pump reservoir to the catheter tip.

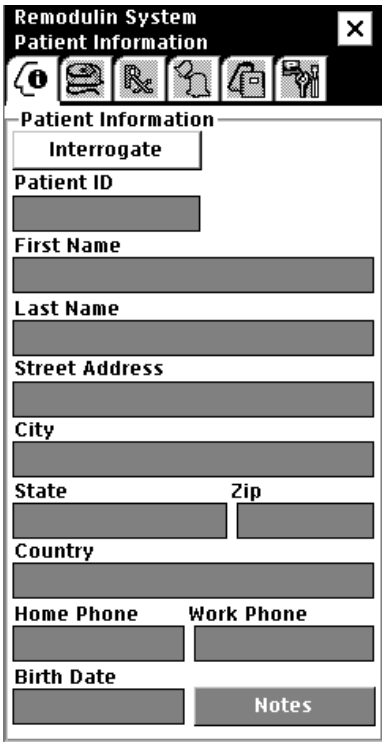
1. If the programmer was shut off, turn the programmer back on and re-interrogate the pump.
2. From the Pump Status screen, confirm that there are no active alarm events.
3. Select the OK button to close the Pump Status screen.

11.2.2 Enter additional patient information

1. Select the Patient Information screen tab.

2. Complete the appropriate patient information (see Figure 46).

Figure 46. Patient information boxes



3. Select Notes and enter 24-hour contact information for the PAH physician.

11.2.3 Program the Prime for New System Implant and the therapeutic rate

1. Select the Infusion screen tab.

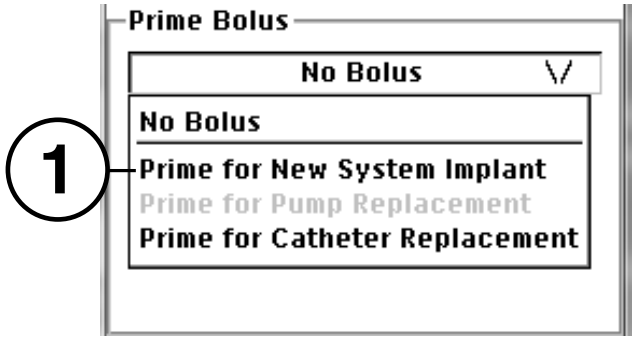
   a. Verify that Remodulin is on the drug button.
   b. Verify that the concentration value is correct.
   c. Verify that the reservoir volume is correct.

2. Select the Mode button and select Simple Continuous from the drop-down list.

   Warning: Confirm the intended drug dosage is selected and programmed. Selecting and programming an incorrect drug dosage may lead to a potential drug overdose or underdose of the patient.

3. Select the Dose button and input the appropriate dose of Remodulin.
4. Select the Dosing Weight button and input the appropriate dosing weight.
5. Select the Prime Bolus button and select Prime for New System Implant from the drop-down list (see Figure 47).

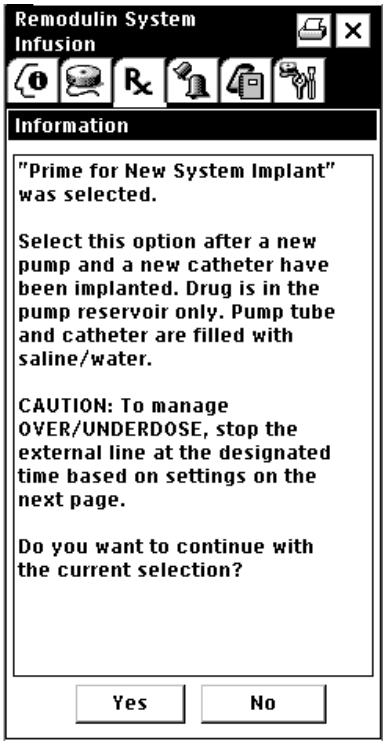
Figure 47. Prime for New System Implant



1 Prime for New System Implant selection

6. Read the information screen and verify that the Prime for New System Implant is appropriate (see Figure 48).

Figure 48. Prime for New System Implant verification

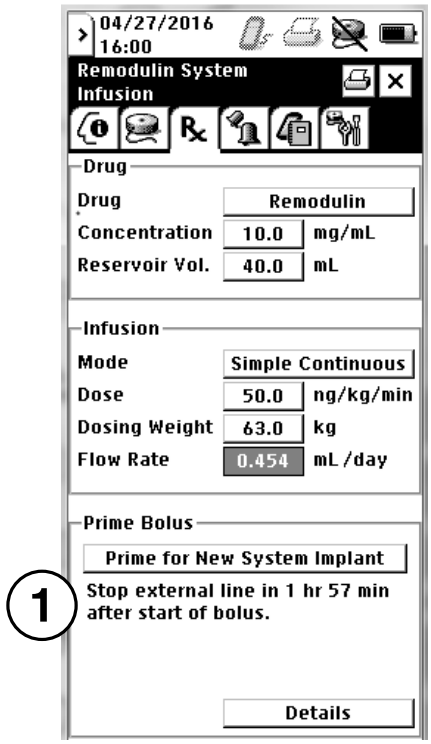


7. Select the Yes button.

   Warning: To avoid a drug overdose or underdose of the patient, stop the flow of Remodulin through the external line at the designated time when the dose from the implanted system reaches 20% (nominal).

   a. Record the time duration to stop the external line displayed on the screen (see Figure 49).

Figure 49. Time duration to stop external line



1 Time duration to stop external line

b. Select the Details button for more information on how the dose from the implanted system and the external line changes during and after the Prime for New System Implant, when to stop the external line after the start of the Prime for New System Implant, or to change the delivered dose percentage when the external line is turned off.

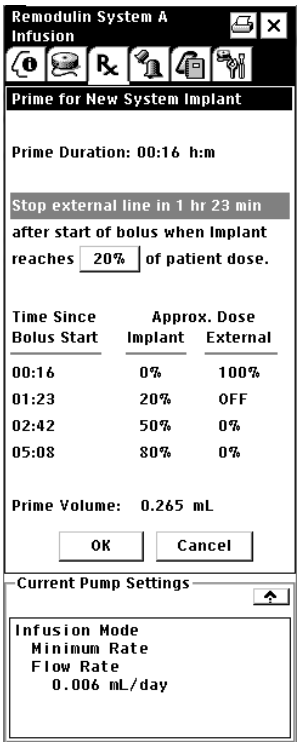
   20% patient dose is the nominal setting to stop the external line (see Figure 50).

   Warning: If the patient dose value is changed from 20%, the time duration to stop the external line changes. Re-record the time duration to stop the external line and stop the external line at that time. Failure to take this action may result in a drug overdose or underdose of the patient.

   The time to stop external line may be changed by selecting the 20% button and selecting a different value.

c. Select the OK button to close the Details window (see Figure 50).

Figure 50. Prime for New System Implant details



8. Select the Summary screen tab.

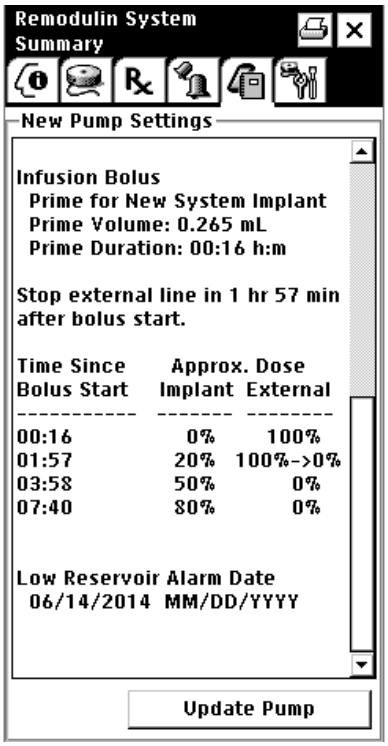
9. Review the New Pump Settings and verify that all information is correct (see Figure 51).

   Warning: Properly record the Low Reservoir Alarm Date. An incorrectly recorded date may cause the scheduled refill date to occur after the pump reservoir has emptied, which may result in underdosing of the patient because of the abrupt cessation of therapy.

   a. Verify that the Low Reservoir Alarm Date approximately matches the planned refill interval. If the alarm date and refill interval do not match, review and correct all programming settings.

   b. If any settings are incorrect, navigate to the appropriate tab and change the setting.

Figure 51. New Pump Settings



10. Select the Update Pump button. The Stop External Line information message is displayed.
    a. Record the time duration to stop the external line.

       Note: The bolus start time begins when the update is complete.

    b. Select the OK button.
11. Select the Yes button to accept the changes and proceed to the Update Pump dialog box.
    a. When the Update Pump dialog box appears, position the programming head over the pump.
    b. Hold the programming head over the pump and select the OK button. Verifying the update can take up to a minute.

c. Select the OK button to complete the update.

d. Wait until the update is completed.

Warning: Closely monitor the patient during the transition of Remodulin delivery from the external line to the implanted system. A drug overdose or underdose of the patient may occur and may require medical management of the patient. If signs of overdose occur, the external line may be turned off earlier than the calculated time provided by the programmer.

12. When the update is complete, start a timer to track when to stop the external line. Record the start time of the Prime for New System Implant and when to stop the external line.
13. Stop the external line at the recorded time.

11.2.4 Administration

Warning: Verify that the scheduled refill date is on or before the Low Reservoir Alarm date. An incorrect refill date may cause the alarm to sound and underdosing of the patient to occur.

1. Print out the patient's prescription and current pump settings (pump status).
2. Place the prescription and pump settings into the patient's records.
3. Determine the refill date from the printout.
4. Schedule a refill appointment.

12 Alarm programming

Warning: An alarm may not sound under all conditions of pump failure. Patients should be trained to closely monitor their symptoms and contact their managing clinician should any change in symptoms occur.

Warning: Failure of the patient to hear or distinguish a critical alarm may result in underdosing due to conditions that cause abrupt cessation. These conditions may include situations where the pump has been emptied, where the pump has reached end of service (EOS), where a motor stall has occurred, or where a critical memory error in the pump memory has occurred. Ensure that the patient can hear a pump alarm and can distinguish between a critical alarm and a non-critical alarm. If the patient cannot hear a critical alarm, the patient's caregiver should notify the patient.

Caution: Failure of the patient to hear or distinguish a non-critical alarm may lead to situations that require attention by the clinician. These conditions may include situations where the pump is low, where the pump needs to be replaced, or where a non-critical pump memory error has occurred. Ensure that the patient can hear a pump alarm and can distinguish between a critical alarm and a non-critical alarm. If an alarm sounds and the patient cannot hear it, the patient's caregiver should notifiy the patient.

12.1 Testing alarms

It is recommended that a pre-discharge alarm test be done so that the patient or patient's caregiver is aware of the different alarm tones for critical and non-critical alarms.

Note: When the patient is in the clinic for refill visits, test the alarms at least annually to remind the patient what the alarms sound like.

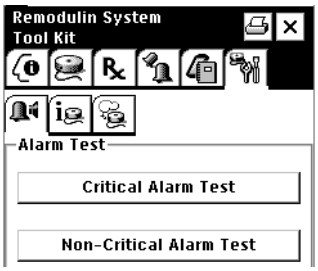
1. If the programmer was shut off, turn the programmer back on and re-interrogate the pump.

   Note: The patient must be conscious for this test.

2. Select the Tool Kit screen tab.

3. Select the Alarm Test tab (see Figure 52).

Figure 52. Alarm Test tab



12.1.1 Critical alarm test

1. Select the Critical Alarm Test button.
2. When the Alarm Test dialog box appears, position the programming head over the pump.
3. Hold the programming head over the pump and select the OK button. Once telemetry is complete, the Telemetry Complete message appears. The programmer sounds a telemetry complete tone. Within seconds of the tone, the pump sounds the critical alarm.
4. Verify that the patient is able to identify the critical alarm tone.
5. Select the OK button.

12.1.2 Non-critical alarm test

1. Select the Non-Critical Alarm Test button.
2. When the Alarm Test dialog box appears, position the programming head over the pump.
3. Hold the programming head over the pump and select the OK button. Once telemetry is complete, the Telemetry Complete message appears. The programmer sounds a telemetry complete tone. Within seconds of the tone, the pump sounds the non-critical alarm.
4. Verify that the patient is able to identify the non-critical alarm tone.
5. Select the OK button.

12.2 Changing low reservoir alarm volume

Note: The extracted volume from the reservoir is prone to measurement errors, causing variation in the volume from one refill to another. Consider the extracted volumes from multiple refills before changing the low reservoir alarm volume.

The default setting for a new pump is 4 mL. Changing the low reservoir alarm volume changes the calculated reservoir fluid volume at which the low reservoir alarm is activated. If the volume of Remodulin® (treprostinil) Injection extracted from the pump is greater than or equal to the expected reservoir volume, the low reservoir alarm volume may be decreased.

1. Interrogate the pump, if necessary.
2. Select the Alarms screen tab.

3. Select the Low Reservoir Alarm Volume button.

   Warning: Decreasing a reservoir alarm volume too aggressively can lead to actual reservoir volumes of less than 1 mL, which can result in underinfusion and the return of symptoms, including a drug underdose for the patient.

4. Enter the desired low reservoir alarm volume.
5. Select the OK button.
6. Review the alarm settings.
7. Update the pump (see Section 9.3).

12.2.1 Administration

Warning: Verify that the scheduled refill date is on or before the Low Reservoir Alarm date. An incorrect refill date may cause the alarm to sound and underdosing of the patient to occur.

1. Print out the patient's prescription and current pump settings (pump status).
2. Place the prescription and pump settings into the patient's records.
3. Determine the refill date from the printout.
4. Schedule a refill appointment.

12.3 Changing the alarm interval

Changing the alarm interval controls the frequency that the alarm sounds, if it is activated.

1. Interrogate the pump, if necessary.
2. Select the Alarms screen tab.

3. Select the Critical Alarm Interval button.
4. Select the alarm interval from the drop-down list.
5. Select the Non-Critical Alarm Interval button.
6. Select the alarm interval from the drop-down list.
7. Update the pump (see Section 9.3).

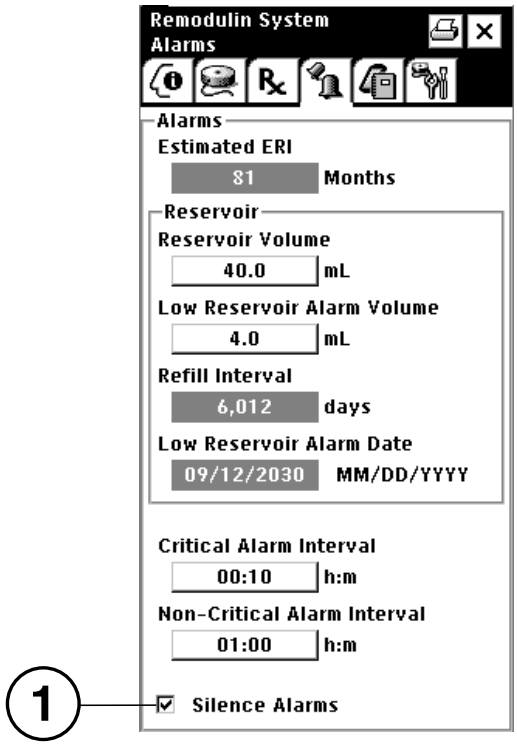
12.4 Silencing the alarms

This feature is only available if the pump is generating a critical or non-critical alarm at the time the pump is being interrogated.

1. Interrogate the pump, if necessary, and close the alarm dialog box, if necessary.
2. Select the Alarms screen tab.

3. Select the Silence Alarms box (see Figure 53).

Figure 53. Silence Alarms box



1 Check mark appears in the Silence Alarms box

4. Update the pump (see Section 9.3).

13 Pump refill or changes to Remodulin therapy

13.1 Refilling and programming the pump

Use the Medtronic Model 8551 Refill Kit when refilling the pump with Remodulin® (treprostinil) Injection. Follow the refill procedure as outlined in this chapter for Remodulin refills.

Warnings:

- Failure to follow refill instructions can result in leakage of Remodulin into the subcutaneous tissue. Leakage of Remodulin into the subcutaneous tissue may result in local reactions and potentially systemic reactions. Local reactions due to side effects of Remodulin include pain, erythema, and swelling. Systemic reactions due to side effects of Remodulin overdose include flushing, headache, nausea, and hemodynamic changes.
- Monitor the patient for one hour after the refill procedure. Refill reactions may occur during needle removal as a result of Remodulin that forms at the needle tip as the needle is retracted from the subcutaneous tissue. This may result in local reactions at the pump refill site and potentially systemic reactions. Local reactions due to side effects of Remodulin may include pain, erythema, and swelling. Systemic reactions due to Remodulin overdose may include flushing, headache, nausea, and hemodynamic changes. Chilling Remodulin is intended to reduce the incidence and magnitude of the refill reaction.

Caution: Remodulin refills should only be performed with immediate access to trained personnel and equipment to administer advanced cardiac life support.

Note: When the patient is in the clinic for refill visits, test the alarms occasionally to remind the patient what the alarms sound like.

13.1.1 Sterilization

All components of the kit are sterile. Do not resterilize. Should sterility of the kit be in question, discard and use a new kit.

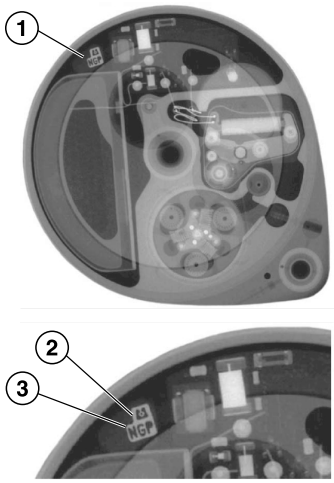
13.1.2 Preliminary procedures

1. Gather the following sterile equipment from the refill kit:
   - extension set with a clamp
   - 0.22 micron filter
   - 22-gauge noncoring needle
   - 20 mL empty syringe
   - fenestrated drape
   - template
2. Gather the following locally supplied equipment:
   - syringes containing prescribed Remodulin
   - cleansing agent
   - sterile gloves
   - alcohol pads or swabs
   - adhesive bandage (optional)
   - programmer (N'Vision Model 8840 Clinician Programmer with 8870 Application Card)
3. Verify that a crash cart is available.
4. Refer to the Remodulin drug labeling for indications, contraindications, warnings, precautions, dosage and administration information.
5. Prepare the programmer for use.
6. Interrogate the pump. Put a check mark in the Logs box. Refer to Section 9.1 for detailed instructions on interrogating the pump.
7. Confirm:
   - the pump model
   - the reservoir volume
   - the location of the pump

   Note: Review the Event log to confirm that there are not any unanticipated events. Refer to Table 16 for a detailed description of Event log messages.

   The model and reservoir volume can be confirmed by the programmer. Alternatively, a radiopaque identifier in the pump shows the pump model and identifies Medtronic as the pump manufacturer on a standard x-ray (see Figure 54). A three-letter code designates the pump model.

Figure 54. A radiopaque identifier on a pump



1 Radiopaque identifier
2 Medtronic symbol
3 Medtronic designator

8. Confirm that the volume of the prescribed fluid does not exceed the reservoir volume of the pump.

13.1.3 Chilling Remodulin

Note: Chilling Remodulin is required to decrease the risk of subcutaneous exposure of Remodulin, which resulted in adverse events during the clinical trial.

Before using Remodulin, refrigerate or chill the Remodulin vials on wet ice for a minimum of 30 minutes before injecting Remodulin into the pump reservoir.

Transfer and maintain Remodulin vials on wet ice until necessary to fill injection syringes and inject into the pump reservoir.

Chilling Remodulin vials prior to injecting Remodulin into the pump reservoir may reduce the potential for site reactions during needle removal at the injection site.

Remodulin should only be chilled one time. Remodulin that has been chilled and returned to room temperature should not be re-chilled.

13.1.4 Verify current pump settings

Before starting the refill procedure, verify the following pump and patient prescription settings:

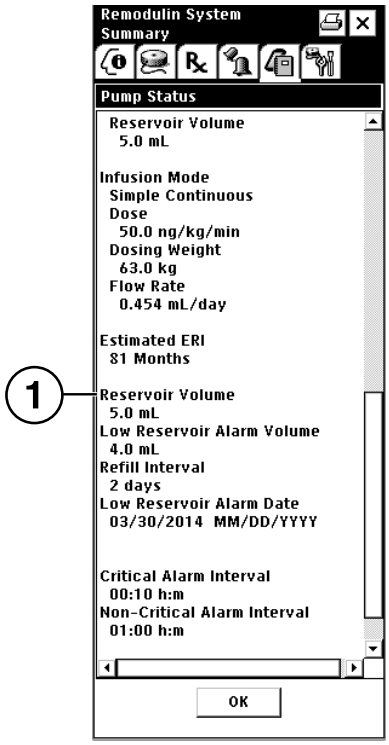
1. Turn on the programmer and interrogate the pump. Put a check mark in the Logs box. Refer to Section Section 9.1 for detailed instructions on interrogating the pump. Confirm the following from the Pump Status screen:
   - There are no active alarm events.
   - Pump model number and volume capacity of the pump's reservoir are correct.
   - The pump reservoir volume capacity is equal to, or greater than, the planned refill volume of Remodulin.
   - Confirm that the Remodulin concentration is the same as the planned refill concentration of Remodulin.
   - The Infusion Mode is Simple Continuous.
   - Dose and Dosing Weight are appropriate for the patient.
   - The estimated Elective Replacement Indicator (ERI) is adequate.

   Note: Review the Event log to confirm that there are not any unanticipated events. Refer to Section A.7 for a detailed description of Event log messages.

2. Record the Reservoir Volume (expected reservoir volume) from the Pump Status screen (see Figure 55).

   Note: Review the pump logs to verify proper functioning of the device.

Figure 55. Reservoir Volume



1 Reservoir Volume to be recorded

3. Select the OK button to close the Pump Status screen.

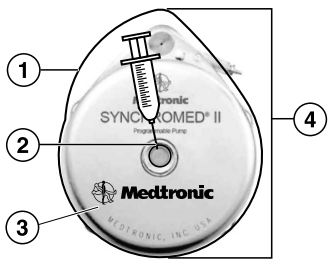
13.1.5 Empty the pump

1. Prepare the injection site by cleansing the area.
2. Open the kit. Put on sterile gloves.
3. Place the drape, exposing the pump site.
4. Using sterile procedures, assemble the needle, extension set, and empty syringe as follows:
   a. Connect the empty syringe to the extension set (see Figure 58).
   b. Connect the needle to the extension set.

5. Palpate the pump and identify the location of the catheter access port and the edges of the pump. Factors that may make it difficult to locate the pump include, but are not limited to:
   - deep implant
   - patient position (for example, a seated patient)
   - scar tissue at the pump implant site
   - seroma
   - pump is tilted in the pocket
   - obesity
   - pump movement within the pocket
   - weight gain after implant
   - weight loss after implant

   If you have difficulty identifying the pump features, you may seek assistance from another clinician. If deemed necessary by the clinician, x-ray and fluoroscopy can be used to assist in locating or determining the orientation of the pump.
6. Place the template on the skin over the pump (see Figure 56). Align the right edge of the template with the right edge of the pump. Use the center circle of the template to insert the needle into the reservoir fill port.

Figure 56. Alignment of the refill template



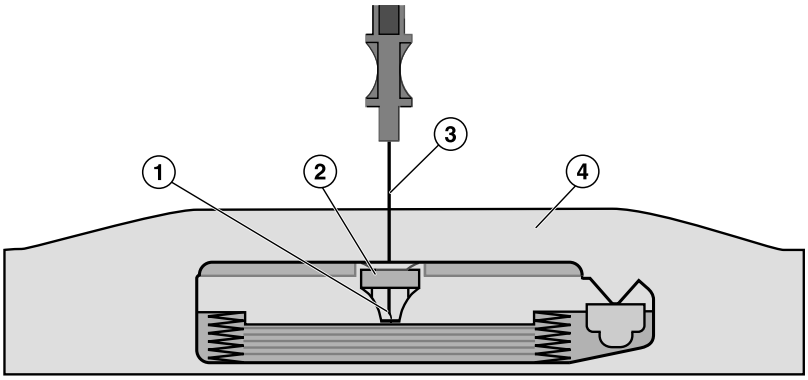
1 Template
2 22-gauge needle
3 Pump
4 Right edge of the template aligned with the right edge of the pump

7. Close the clamp.

8. Gently insert the 22-gauge needle perpendicular to the surface of the pump through the center of the template and into the center of the reservoir fill port until the needle touches the bottom of the reservoir fill port (see Figure 57 and Figure 58).

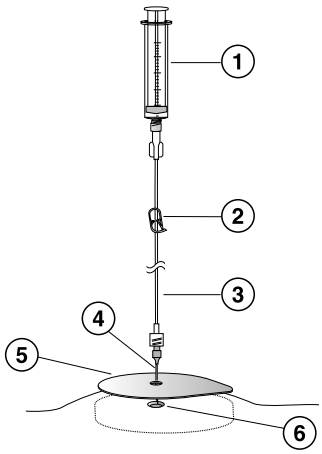
   Note: The pump may be tilted within the pocket and therefore the needle angle may not be perpendicular to the patient's body.

Figure 57. Inside view of a pump with the needle fully and properly inserted



1 Bottom of the reservoir fill port
2 Septum
3 Needle
4 Subcutaneous tissue

Figure 58. Clamp closed and needle inserted into the reservoir fill port



1 Empty syringe
2 Closed clamp
3 Extension set
4 Needle

5 Template
6 Reservoir fill port

During proper needle insertion, you will feel the needle:

- pass through the patient's skin and subcutaneous tissue,
- hit the silicone septum (scar tissue, if present, can feel similar to the septum),
- pass through the septum, and
- hit the metal bottom of the reservoir fill port. (The top of the pump is metal and hitting the top of the pump can feel similar to hitting the bottom of the reservoir fill port.)

  If excessive resistance is encountered during needle insertion, reassess placement. Do not force the needle. The feel of abnormal resistance during the procedure may be an indication that the needle is not in the center of the reservoir fill port.

Note: At any point during the procedure, if in doubt about the needle location, reassess its position. Factors that may contribute to difficulty inserting the needle into the reservoir fill port include, but are not limited to:

- the pump is flipped in the pocket
- deep implant
- patient position (for example, a seated patient)
- patient movement (for example, spasticity, difficulty holding still)
- localized muscle spasms at the pump implant site
- scar tissue at the pump implant site
- seroma
- the pump is tilted in the pocket
- obesity
- pump movement within the pocket
- weight gain after implant
- weight loss after implant

9. Open the clamp and slowly withdraw the fluid from the reservoir into the empty syringe.

   Note: If the withdrawn fluid has an unexpected appearance (for example, evidence of blood), the needle may not be properly inserted into the pump. Also, if the fluid does not have the distinctive smell of Remodulin, the needle may not be correctly placed in the pump reservoir. Verify that the needle is inserted into the pump and not the pump pocket.

10. If the syringe maximum capacity is reached before the reservoir is completely empty, more than one syringe will be needed to empty the pump.
    a. Close the clamp.
    b. Remove the full syringe.
    c. Attach an empty syringe.
    d. Verify that the needle is in the pump reservoir fill port.
    e. Repeat Step 9; then continue to Step 11.
11. Completely empty the pump. When the pump is empty, the bubbles will stop forming and negative pressure in the syringe can be felt.
12. Close the clamp and remove the syringe from the extension set.

    Note: Keep the needle in the reservoir fill port and the clamp closed for the pump refill procedure that follows.

13. Record the amount withdrawn from the pump for entry in the patient's record.
14. Compare the amount withdrawn from the pump to the expected reservoir volume recorded earlier. See the pump programmer for the expected volume. The amount withdrawn should approximately equal the expected volume.
15. Discard the fluid and syringe as appropriate for the fluid content in accordance with institutional policies and applicable regulations.

13.1.6 Refill the pump

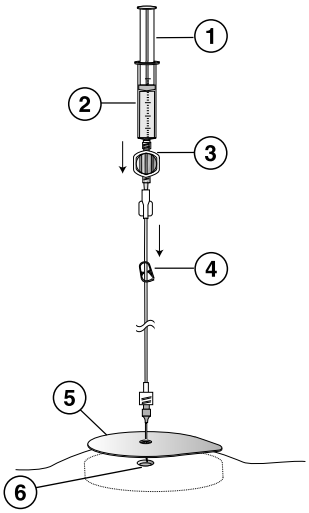
Warning: Pocket fill is the improper injection of Remodulin into the subcutaneous tissue, which includes the pump pocket. A pocket fill can result in a site reaction or a clinically significant drug overdose including hemodynamic collapse or death. Observe the patient for a minimum of 1 hour after the pump refill procedure for any signs or symptoms that could indicate a pocket fill or any other drug-related adverse event due to the refill procedure. Seek emergency assistance. For more information, see Section 8.2.

Warning: Inadvertent injection into the catheter access port may result in a clinically significant or fatal drug overdose. Observe the patient for a minimum of 1 hour after the pump refill procedure for any signs or symptoms that could indicate a drug-related adverse event due to the pump refill procedure. Seek emergency assistance. For more information, see Section 8.2.

Warning: If it is suspected or known that all or part of the drug was injected into the pocket during the refill procedure, monitor the patient closely for signs and symptoms of overdose and seek emergency assistance. Monitor the patient in an appropriate facility for a sufficient amount of time or until the symptoms have resolved. For more information, see Section 8.2.

1. Confirm that the refill volume of the prescribed fluid does not exceed the reservoir volume of the pump.
2. Purge the air from the syringe containing the prescribed fluid.
3. Attach the filter to the syringe with the prescribed fluid.
4. Purge all air from the filter.
5. Attach the syringe with the prescribed fluid and filter to the extension set (see Figure 59).
6. Before and during injection, verify that the needle remains fully inserted to the bottom of the reservoir fill port. Do not apply tension to the extension tubing because the needle may be pulled out from the reservoir.
7. Open the clamp and as the clamp is opened, observe the following indications that the needle continues to be properly positioned:
   - The bubbles in the extension set are immediately drawn into the pump.
   - The plunger may move slightly when the drug is initially drawn into the pump.
8. Slowly depress the plunger on the syringe to inject the prescribed fluid into the pump reservoir. While injecting the prescribed fluid, verify that the needle remains properly located within the reservoir (see Figure 59).
   a. Periodically withdraw and observe a portion of the drug to confirm that the drug has the expected appearance.
   b. After confirming that the needle remains in the reservoir, resume injecting fluid.

Figure 59. Open the clamp and inject into the pump reservoir



1 Plunger
2 Syringe with prescribed fluid
3 Filter
4 Open clamp
5 Template
6 Reservoir fill port

Caution: Do not prematurely activate the pump reservoir valve by overpressurizing the reservoir. Activation of the pump reservoir valve seals the pump reservoir valve closed. Unusual resistance or the inability to inject the entire fill volume may indicate activation of the pump reservoir valve. If the valve closes, the reservoir contents must be delivered or removed before completing the filling of the pump. Procedural delays can occur.

To prevent activation of the pump reservoir valve during emptying and filling procedures:

- completely aspirate all contents of the pump reservoir before filling;
- do not allow air into the pump reservoir through an open needle in the septum or an unclamped extension; and
- do not exceed the maximum reservoir volume indicated in the pump labeling.

9. If you have activated the reservoir valve, complete Steps a through g that follow. Otherwise, proceed to Step 10.
   a. Discontinue injection.
   b. Close the clamp.

c. Remove the syringe with prescribed fluid and attached filter.

d. Attach an empty 20 mL syringe to the extension set.

e. Open the clamp and aspirate until all fluid and air are removed.

f. Close the clamp and remove the syringe containing the aspirate from the extension set and discard the syringe.

g. Repeat Steps 2 through 10.

10. If more than one syringe of prescribed fluid is needed to fill the pump reservoir, complete Steps a through d that follow. Otherwise, proceed to Step 11.

    a. Close the clamp.

    b. Keep the filter from the extension set in place, and remove the first syringe from the filter.

       Caution: Do not remove the filter from the extension set. Removal of the filter could compromise the sterile barrier, which could result in an infection for the patient.

    c. Purge the air from the second syringe, and attach the second syringe to the filter (see Figure 59).

    d. With the second syringe in a vertical position, open the clamp and slowly depress the plunger on the syringe to inject the prescribed fluid into the pump reservoir.

11. When filling is complete, close the clamp and carefully remove the needle from the reservoir fill port.

    Note: If you are unsure whether drug was injected correctly into the pump, completely aspirate the pump to verify that all of the injected drug can be removed.

12. Remove the cleansing agent from the patient's skin using an alcohol pad.

13. Apply an adhesive bandage, if desired.

14. Discard all components of the kit.

13.1.7 Program the pump

Note: At every patient visit, the clinician must review the Event log for any pump failures that have occurred since the last visit.

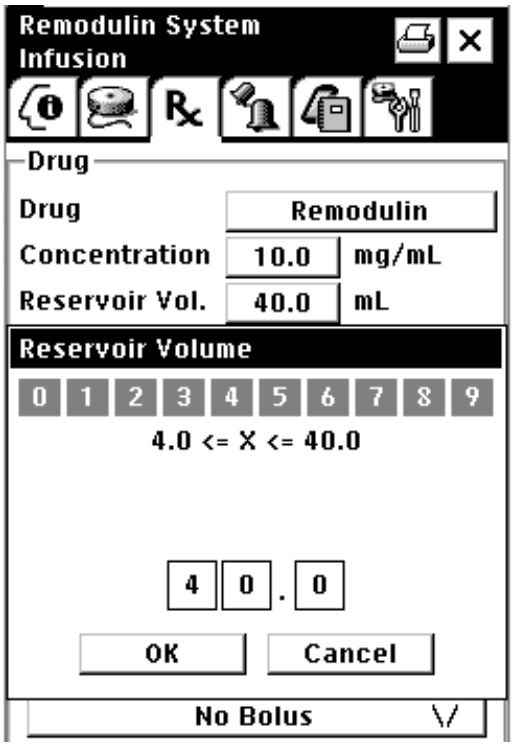
1. If the programmer is off, turn the programmer back on and interrogate the pump.
2. Confirm the following from the Pump Status screen:
   - There are no active alarm events.
   - Pump model number and volume capacity of the pump's reservoir are correct.

- Current pump settings are accurate for the patient.
- The estimated Elective Replacement Indicator (ERI) is adequate.

3. Select the OK button to close the Pump Status screen.
4. Select the Infusion screen tab.

5. Select the Reservoir Vol. button and enter the amount of Remodulin that went into filling the pump. Select the OK button to accept the value (see Figure 60).
6. Verify the new Reservoir Volume on the programmer screen.

Figure 60. Reservoir Volume input box



7. Select the Summary screen tab.

8. Verify that the low reservoir alarm date approximately matches the planned refill interval. If the alarm date and the refill interval do not match, review and correct all programmer settings.
9. Update the pump (see Section 9.3).

13.1.8 Administration

Warning: Verify that the scheduled refill date is on or before the Low Reservoir Alarm date. An incorrect refill date may cause the alarm to sound and underdosing of the patient to occur.

1. Print out the patient's prescription and pump settings (pump status).
2. Place the prescription and pump settings into the patient's records.
3. Determine the refill date from the printout.
4. Schedule a refill appointment.
5. Observe the patient for a minimum of 1 hour following a pump refill.

To change the Remodulin dose or the dosing weight, follow the instructions in Section 13.2 or Section 13.3.

13.1.9 Evaluate reservoir volume

At every refill visit, record and compare the actual removed volume and the expected removed volume of the reservoir. See the pump programmer for the expected volume. The difference between these values may change over the life of the system. Evaluate the accuracy of the drug delivery based on the number of refills.

1. Calculate the accuracy ratio using the following formula.

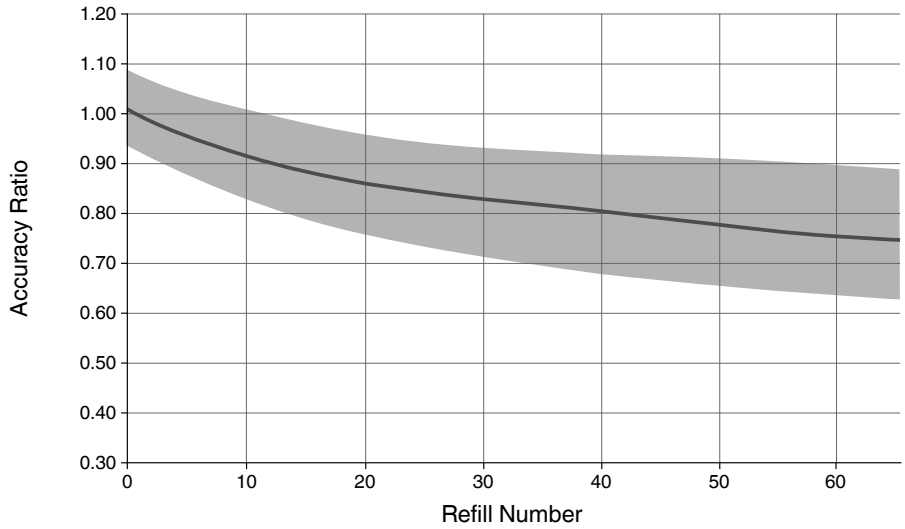
   Figure 61. Accuracy ratio formula

   $$\textit{Accuracy Ratio} = \frac{\textit{Previous fill volume - Actual removed volume}}{\textit{Previous fill volume - Expected removed volume}}$$

   The Previous fill volume is the volume injected into the pump at the last refill. The Actual removed volume is the amount recorded in Section 13.1.5. The Expected removed volume is the Reservoir Volume recorded in Section 13.1.4.
2. Evaluate that the accuracy ratio is within an expected range based on the number of pump refills. See Figure 62 if refilling 40 mL at a time. If the accuracy ratio is outside of the expected range, contact Technical Services at the number listed in Section 2.4.

Note: Note that these graphs only apply to the Implantable System for Remodulin and should not be used for intrathecal therapies.

Figure 62. Implantable System for Remodulin expected accuracy ratio for a 40 mL refill volume. The shaded area represents the DellVery for PAH clinical trial refill accuracy data (95/95% tolerance interval of the exponential data model).



13.2 Changing the Remodulin dose

1. Interrogate the pump and obtain the Event log data, if necessary.

   Note: Review the Event log to confirm that there are not any unanticipated events. Refer to Table 16 for a detailed description of Event log messages.

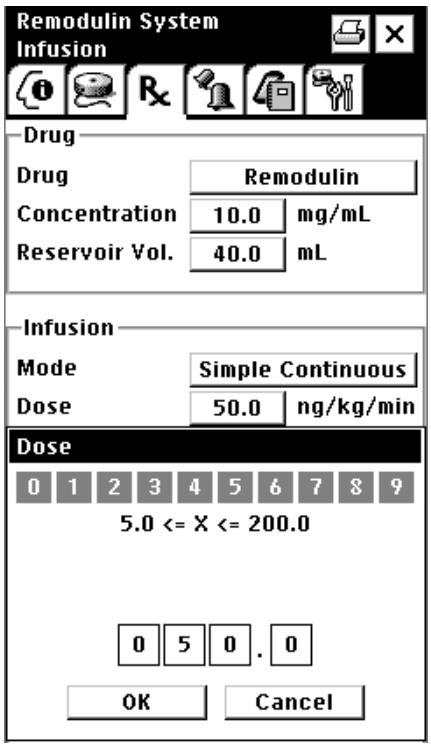
2. Select the Infusion screen tab.

Warnings:

- Do not change the dose without consulting the PAH managing physician. The change in dose may cause a drug overdose or underdose of the patient.
- Confirm that the intended drug dosage is selected and programmed. Selecting and programming an incorrect drug dosage may lead to a potential drug overdose or underdose of the patient.

3. Select the Dose button and enter the new dose of Remodulin.
4. Select the OK button to accept the value (see Figure 63).

Figure 63. Infusion Dose



5. Update the pump (see Section 9.3).

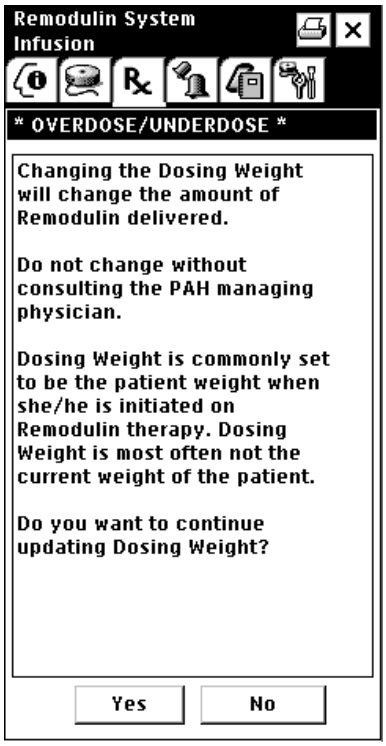
13.3 Changing the dosing weight

1. Interrogate the pump, if necessary.
2. Select the Infusion screen tab.

Warning: Do not change the dosing weight without consulting the PAH managing physician. The change in dosing weight may cause a drug overdose or underdose for the patient.

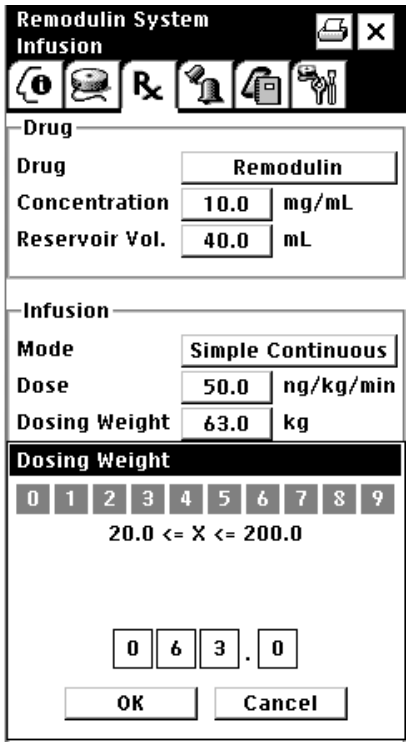
3. Select the Dosing Weight button.
   a. Review the information and verify that the change in dosing weight is appropriate for the patient (see Figure 64).
   b. Select the Yes button to proceed with changing the dosing weight.

Figure 64. Dosing Weight information



4. Enter the new dosing weight. Select the OK button to accept the value (see Figure 65).

Figure 65. New Dosing Weight



5. Update the pump (see Section 9.3).

14 Pump replacement

14.1 Preparing for pump replacement

1. The pump replacement procedure assumes an external supply of Remodulin is not needed because of the short procedure time. The clinical decision regarding starting an external line of Remodulin before the pump replacement procedure should consider:
   - When in the replacement procedure the implanted pump will be programmed to Minimum Rate.
   - The time needed to prepare an external intravenous source of Remodulin if the pump replacement procedure takes longer than expected due to damage to the implanted catheter.
2. Obtain the appropriate prescription dosage of Remodulin® (treprostinil) Injection in ng/kg/min and dosing weight in kg. Consider the patient specific accuracy ratio from the last few refills to determine dose by weight (ng/kg/min) for the new pump.
3. Consider the following when assessing if the pump size and concentration are suitable for the patient's body size:
   - Ability of patient's anatomy to accept the weight and bulk of the pump
   - Pump refill interval (see Appendix B).
   - Pump longevity (see Appendix B).
4. Determine the amount (volume) of Remodulin for initial pump fill. Include an additional 10 mL of Remodulin to rinse the pump as part of preparing the pump for implant.

14.2 Assembling system components and supplies for the new pump

Assemble the following sterile and non-sterile components and supplies:

- SynchroMed II Programmable Pump for the Implantable System for Remodulin 8637P40
- Remodulin, 2 or 3 vials
- sterile saline
- 20 mL syringes (2)
- 3 mL syringes (2)
- 20- to 22-gauge needles (2)

- sterile sleeve
- extension set with clamp
- 0.22 micron filter
- N'Vision Model 8840 Clinician Programmer with the Model 8870 Application Card

14.3 Preparing the new pump

Implanting physicians should be experienced in pump and catheter implant procedures and should be thoroughly familiar with all product labeling. Preparing the pump for implant involves establishing telemetry between the programmer and the pump. For general information on establishing telemetry between the programmer and the pump, to obtain pump status information, and to begin a new programming session, see Section 9.1.

Cautions:

- Do not implant a pump that has been dropped onto a hard surface or shows signs of damage. Implanting a pump that has been dropped or damaged can result in unintended therapy, including a potential drug overdose or underdose of the patient, and requires additional surgery to replace the pump.
- Do not implant the pump unless pump operation has been confirmed. Failure to confirm pump operation before implant can result in additional surgery to replace the pump.
- Do not prematurely activate the pump reservoir valve by overpressurizing the reservoir. Activation of the pump reservoir valve seals the pump reservoir closed. Unusual resistance or the inability to inject the entire fill volume may indicate activation of the pump reservoir valve. If the valve closes, a portion of the reservoir contents must be delivered or removed before completing filling the pump. Procedural delays can occur. To prevent activation of the pump reservoir valve during emptying and filling procedures, take the following actions:
  - Completely aspirate all contents of the pump reservoir before filling.
  - Do not allow air into the pump reservoir through an open needle in the septum or an unclamped extension.
  - Do not exceed the maximum reservoir volume indicated in the pump labeling.
- The programmer and the programming head are not sterile. To use the programmer in a sterile field, place the programming head inside a sterile sleeve before passing it into the sterile field. This action places a sterile barrier between the patient and the programming head, preventing infection. Do not sterilize any part of the programmer. Sterilization may damage the programmer or the programming head.
- Install and use the filter at the indicated steps. The filter prevents air in the syringe or tubing from entering the pump reservoir and filters foreign material, including bacteria, from entering the reservoir. Air in the reservoir may prevent the pump from properly filling and may cause activation of the pump reservoir valve seal before the pump is completely filled with drug. Unfiltered foreign material or bacteria may result in contaminated drug and may lead to a systemic infection.
- Monitor the patient for symptoms of overdose, underdose or worsening symptoms. Infusion variability between the old pump and the new pump may be observed as a change in patient symptoms related to either overdosing or underdosing and may require an adjustment in dosing.

14.3.1 Prepare to empty the new pump

Warning: The calibration constant displayed on the programmer screen after reading the pump status must match the calibration constant printed on the shelf package. If calibration constants differ, contact the appropriate representative listed in Section 2.4. Using an incorrect calibration constant may result in a clinically significant or fatal drug underdose or overdose of the patient.

1. Before opening the shelf package, position the programming head over the target symbol on the bottom of the pump package. Use the programmer to interrogate the pump and confirm the following from the Pump Status screen:
   - pump battery status
   - current pump settings
   - no active alarm events. If the pump is still in Shelf State, audible alarms are disabled. The pump must be interrogated to determine if an alarm has been activated.
   - pump calibration constant (Cal. Constant) displayed on the screen matches the calibration constant printed on the shelf package
2. Select the OK button to close the Pump Status screen.
3. Open the pump shelf box. Remove the FOR YOUR RECORDS label from the pump shelf box and attach the label to the patient's record. This label displays the pump model number, the reservoir size, the calibration constant, and the serial number.

14.3.2 Sterile procedure

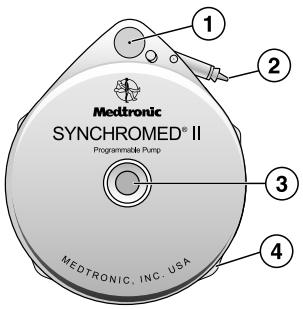
1. Once a sterile table is available and the sterile field is established, pass the sterile pump package and sterile accessories into the sterile field.
2. Open the sterile pump package and remove the pump.
3. Remove the protective cap from the catheter port. (A small amount of water may be present in the protective cap.)

14.3.3 Empty the new pump

Caution: Ensure tubing is clamped at the steps where indicated to prevent introduction of air into the pump reservoir and to prevent water or drug from returning to the pump. Air in the reservoir may prevent the intended amount of drug from being dispensed into the reservoir and may cause the reservoir valve to activate before the pump is completely filled with drug.

1. Assemble the 22-gauge, noncoring needle (black sheath) from the pump package to the extension tubing with clamp.
2. Attach an empty 20 mL syringe to the extension tubing with clamp.
3. Close the clamp.
4. Insert the needle into the reservoir fill port until the needle touches the metal needle stop (see Figure 66).

Figure 66. Pump exterior view



1 Catheter access port	3 Reservoir fill port
2 Catheter port on the pump	4 Suture loop

5. Open the clamp on the extension tubing.
6. Withdraw the sterile water from the pump into the empty syringe (the pump is shipped nearly full).
7. If the volume of fluid in the pump reservoir exceeds the volume of the syringe used for emptying, close the clamp on the extension tubing and remove the filled syringe. Attach an empty syringe, open the clamp on the extension tubing, and repeat until the pump reservoir is empty.
8. Empty the pump reservoir until air bubbles no longer appear in the syringe, ensuring that all water and air are removed from the pump reservoir.
9. If another syringe is required, repeat the process with an additional syringe.
10. Close the clamp on the extension tubing and remove the syringe from the extension tubing.

14.3.4 Rinse the new pump reservoir

Caution: If the water in the pump reservoir is not emptied or the rinse is not performed, the water will mix with the drug when the pump is filled and will dilute the drug in the pump reservoir. As a result the patient will not receive the intended dosage and may experience symptoms of underdosing.

It is recommended that you rinse the pump reservoir twice with 5 mL of Remodulin each time.

Notes:

- The pump reservoir capacity is 40 mL. Because some sterile water remains in the pump reservoir, the final concentration of drug varies based on the fill method (see Table 10).
- The expected concentration of Remodulin in the pump reservoir is based on the assumption that the reservoir is filled to capacity at implant.

Table 10. Expected concentration of drug in the pump reservoir based on fill method

Pump reservoir capacity	Filling without rinsing	Rinsing with 5 mL of drug (x2)
8637P-40	97%	100%

1. Fill a syringe with 5 mL of Remodulin, using the same concentration of Remodulin as intended for the therapy.
2. Attach the filter to the Remodulin-filled syringe and prime the filter.
3. Attach the syringe with filter to the extension tubing and noncoring needle in the reservoir fill port.
4. Open the extension tubing clamp. Slowly inject 5 mL of Remodulin into the reservoir. Close the extension tubing clamp.
5. Remove the syringe with filter from the extension tubing.
6. Attach an empty 20 mL syringe to the extension tubing.
7. Open the extension tubing clamp. Withdraw fluid from the pump reservoir until air bubbles stop flowing into the extension tubing and syringe and negative pressure is felt. Close the extension tubing clamp.
8. Remove the syringe from the extension tubing.
9. Discard the liquid in the syringe.
10. Repeat Step 1 through Step 9 until the 2 rinse cycles are completed.

14.3.5 Fill the new pump

Caution: Do not fill the pump with Remodulin above its labeled capacity of 40 mL. If the pump is overfilled with Remodulin, the actual flow rate exceeds the programmed flow rate and the patient may be overdosed.

1. Fill a syringe or syringes with slightly more than the desired amount of Remodulin.

   Note: Fill the syringe with Remodulin slowly to minimize foaming and air bubbles in the syringe.

2. Attach the filter to the Remodulin-filled syringe and prime the filter.
3. After priming the filter, discard excess Remodulin so the syringe contains the desired amount and does not exceed the capacity of the pump.

   Caution: Ensure that the recorded volume is the actual volume in the syringe after priming the filter. A discrepancy between the volume recorded and the volume dispensed into the pump may lead to an underdose or an abrupt cessation of therapy for the patient.

4. Record the actual fill volume of the syringe.
5. Attach the Remodulin-filled syringe with filter to the extension tubing and noncoring needle in the reservoir fill port.
6. Open the extension tubing clamp.
7. Slowly inject Remodulin into the reservoir.
8. Close the extension tubing clamp.
9. When filling is complete, remove the needle from the pump reservoir fill port.

   Note: If the reservoir valve is activated before the pump is completely filled, follow the steps in Section A.8 to empty the reservoir.

14.4 Programming the new pump on the back table

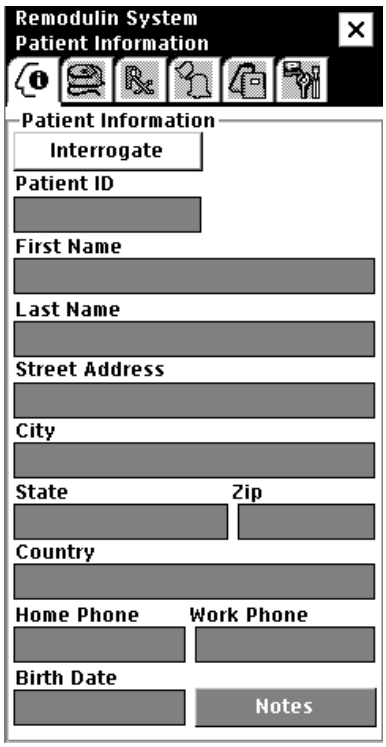
14.4.1 Enter patient information

1. Pass the programming head into the sterile field with the programming head inside a sterile sleeve. If the programmer was shut off, turn the programmer back on and re-interrogate the pump.

2. Enter patient information:
   a. Select the Patient Information screen tab.

   b. Select the appropriate input boxes, and enter patient name, ID number, and any other appropriate patient information (see Figure 67).

Figure 67. Patient Information boxes



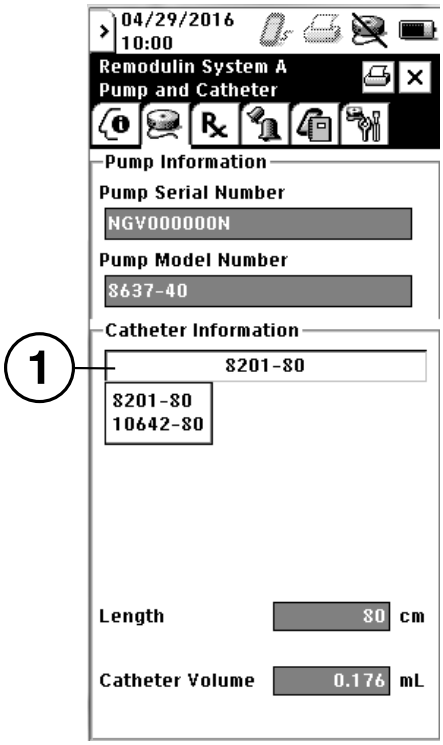
14.4.2 Enter pump and catheter information

Warning: Confirm the intended catheter is selected and programmed. Selecting and programming an incorrect catheter model number may lead to a potential drug overdose or underdose of the patient.

1. Select the Pump and Catheter screen tab.

2. Select the Catheter Information button and select the appropriate catheter from the drop-down list (see Figure 68).

Figure 68. Catheter Information



1 Field showing catheter selected

Once the appropriate catheter is selected, the Length and Catheter Volume fields automatically populate with the correct values.

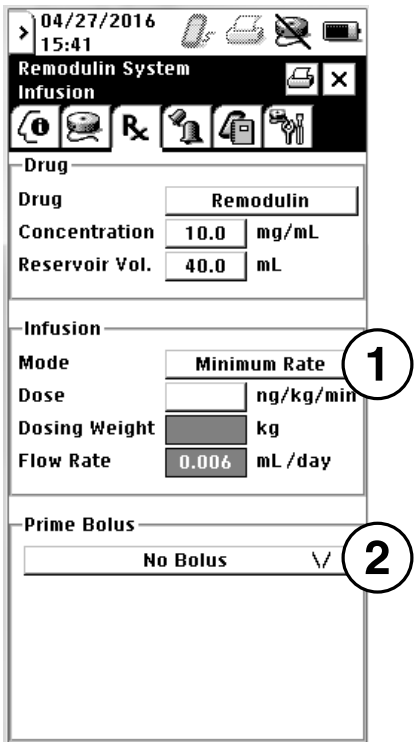
14.4.3 Enter Remodulin information

Warning: Confirm that the intended Remodulin concentration is selected and programmed. Selecting and programming an incorrect Remodulin concentration may lead to a potential drug overdose or underdose of the patient.

1. Select the Infusion screen tab.

2. Select the Drug button and select Remodulin from the drop-down list.
3. Select the Concentration button and select the appropriate concentration from the drop-down list.
4. Select the Reservoir Vol. button and enter the volume of Remodulin that is currently in the pump.
5. Select the OK button to continue. The reservoir volume is displayed on the Reservoir Vol. button.
6. Verify that the Infusion Mode is at Minimum Rate and that the Prime Bolus has No Bolus selected (see Figure 69).

Figure 69. Infusion Mode and Prime Bolus



1 Minimum Rate selected as Mode
2 No Bolus selected under Prime Bolus

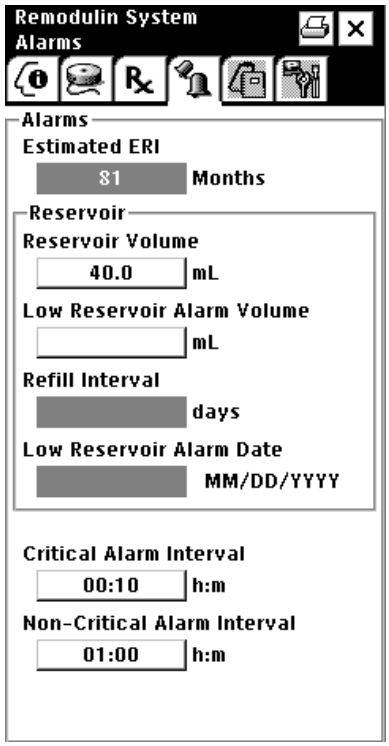
14.4.4 Set the Low Reservoir Alarm Volume

Warning: Adjusting the Low Reservoir Alarm Volume lower than recommended may result in an abrupt cessation of therapy if the pump empties before the alarm is set to sound.

1. Select the Alarms screen tab.

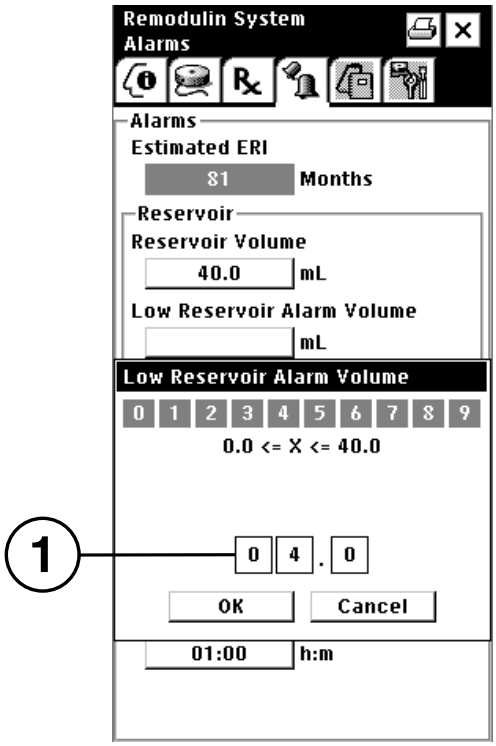
2. Select the Low Reservoir Alarm Volume button (see Figure 70).

Figure 70. Low Reservoir Alarm Volume



3. Confirm that the Low Reservoir Alarm Volume is set to 4.0 (see Figure 71).

Figure 71. Low Reservoir Alarm Volume set to 4.0



1 4.0 selected as the Low Reservoir Alarm Volume

4. Select the OK button to accept the value.

14.5 Prime for Pump Replacement overview

Prime for Pump Replacement is for a pump-only replacement. The catheter is implanted and is filled with Remodulin.

Prime for Pump Replacement must be completed and the catheter access port must be flushed with Remodulin before the pump is joined to the catheter.

Remodulin mixes with the water in the pump tubing during Prime for Pump Replacement. Once the prime is completed, the catheter access port is flushed with Remodulin to clear the diluted Remodulin in the last section of the catheter access port. This procedure ensures that non-diluted drug is present throughout the entire drug pathway of the pump.

14.6 Programming the Prime for Pump Replacement

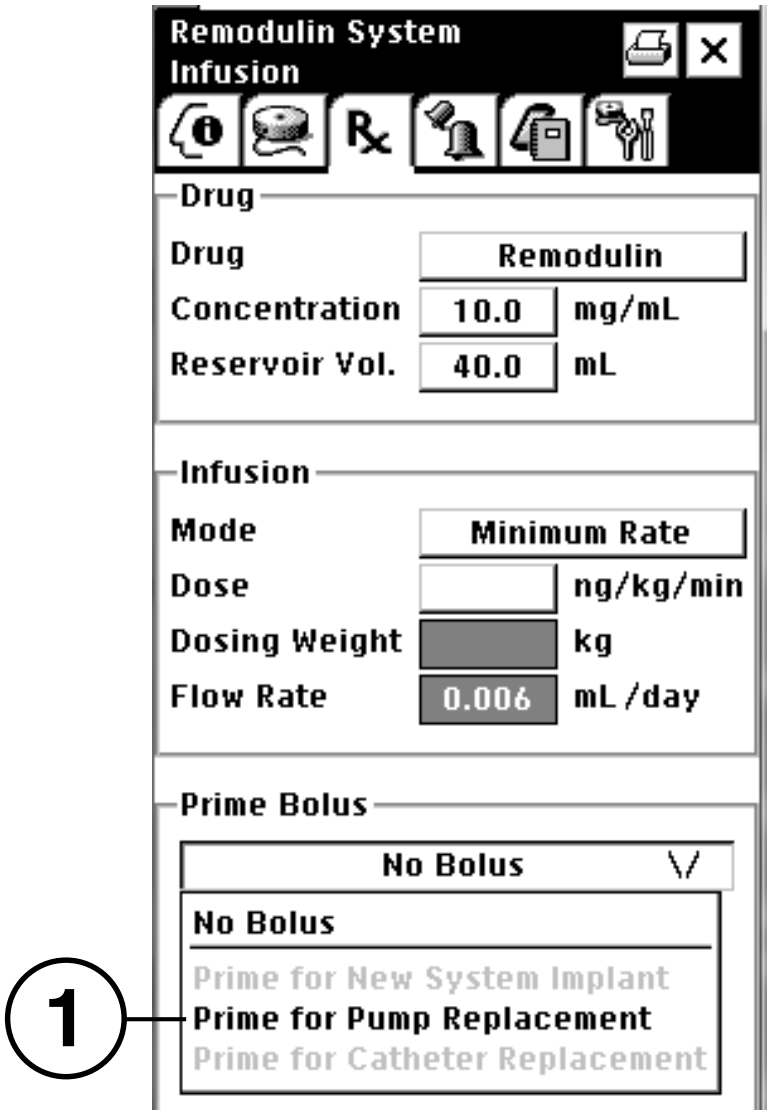
1. Select the Infusion screen tab.

2. Verify that the Mode is set to Minimum Rate.

   Note: Prime for Pump Replacement is only available when the Mode is set to Minimum Rate.

3. Select the Prime Bolus button.
4. Select Prime for Pump Replacement from the drop-down list (see Figure 72).

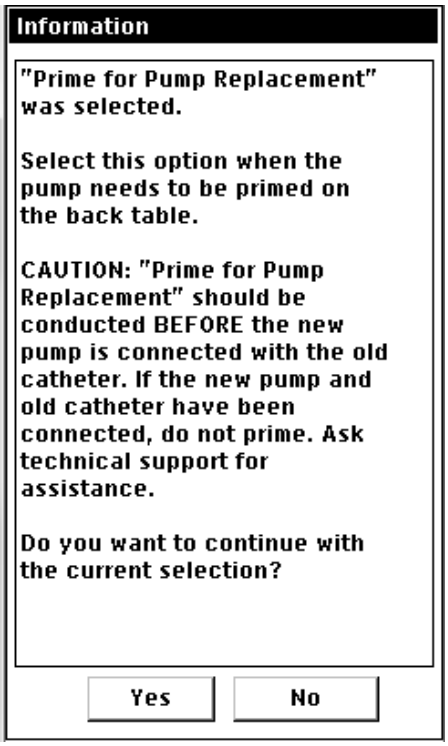
Figure 72. Prime for Pump Replacement



1 Prime for Pump Replacement selected

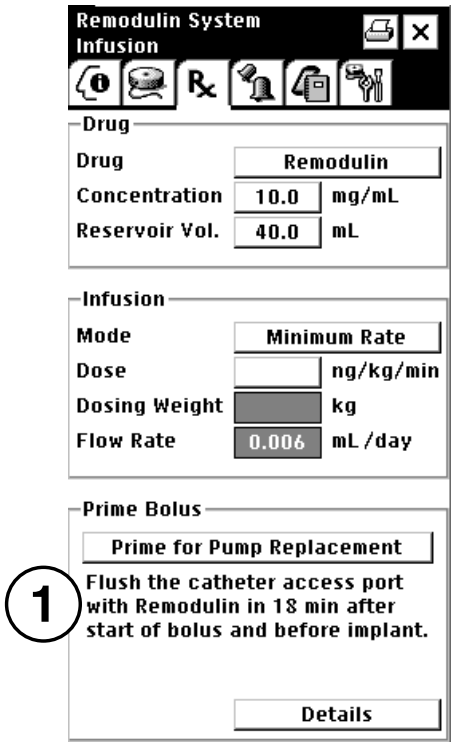
5. Review the information, verify that the change is appropriate for the patient, and then select Yes (see Figure 73).

Figure 73. Prime for Pump Replacement verification



6. Record the time duration for when to flush the catheter access port with Remodulin (see Figure 74).

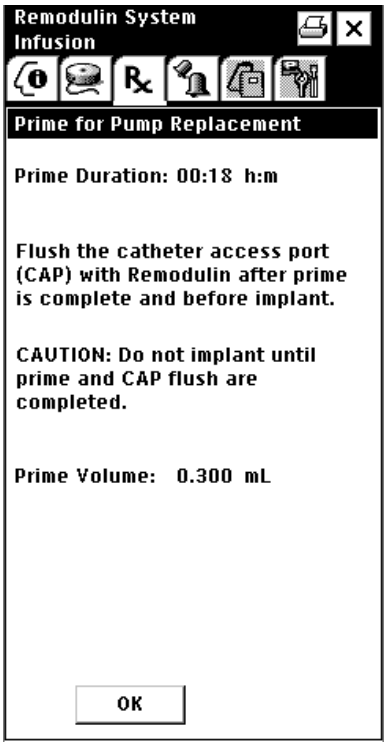
Figure 74. Time duration for flushing the catheter access port



1 Time duration for flushing the catheter access port with Remodulin

7. Select the Details button for more information regarding when to flush the catheter access port (see Figure 75).

Figure 75. Prime for Pump Replacement details

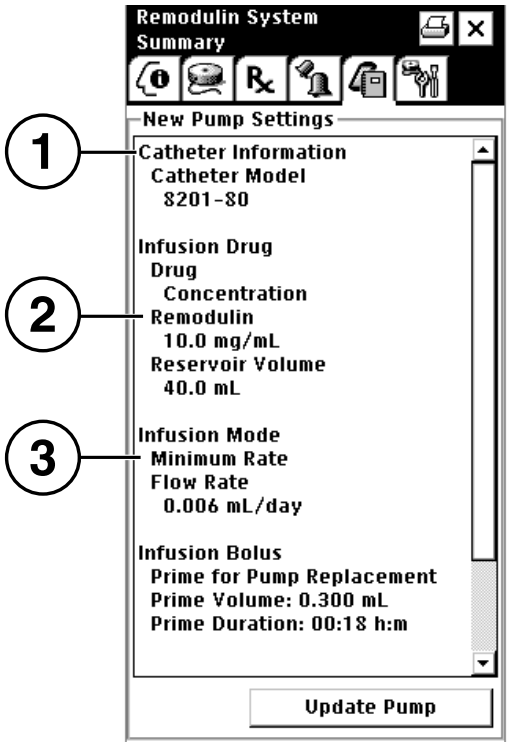


8. Select the OK button to close the Prime for Pump Replacement details window.

14.6.1 Update the pump

1. Update the pump (see Section 9.3, “Updating the pump”, page 61).
2. When the update is complete, start a timer to track when the back table prime is complete. Record the start time of the prime and when the prime will be complete.
3. On the New Pump Settings screen, verify the following information (see Figure 76):
   - The Infusion Mode is set to Minimum Rate
   - The values for the catheter and Remodulin concentration are correct

Figure 76. New Pump Settings



1 Catheter Information
2 Remodulin concentration
3 Infusion Mode set to Minimum Rate

14.6.2 Flush the catheter access port with Remodulin

After the Prime for Pump Replacement is complete, perform the following steps:

1. Fill a 3 mL syringe with 1 to 2 mL of Remodulin.
2. Attach the 24-gauge, noncoring needle (purple sheath) to the syringe.
3. Gently insert the needle into the catheter access port until the needle touches the metal needle stop.
4. Inject Remodulin into the catheter access port.
5. Verify that liquid is coming out of the catheter port on the pump.
6. Remove the needle from the catheter access port.

14.6.3 Remove Remodulin from the exterior of the pump

Warning: Before the pump is implanted in the patient, wipe the exterior of the pump with gauze to remove any Remodulin. Remodulin on the exterior of the implanted pump could cause a local tissue reaction or an overdose of the patient.

1. Use gauze to wipe the exterior of the pump.
2. Confirm that no Remodulin is left on the exterior of the pump.

14.7 Explanting the old pump

Warning: The old pump must be set to Minimum Rate before disconnecting the catheter or explanting the pump. If the pump is not set to Minimum Rate, excess Remodulin could leak from the pump into the subcutaneous tissue and cause an overdose of the patient.

Determine if an external supply of Remodulin is needed.

14.7.1 Removing the old pump from the pocket

1. Use fluoroscopy to view the catheter in the pump pocket.

   Warning: Use care when explanting the pump to prevent damage to the catheter. Inadvertently slicing the catheter may cause Remodulin to leak into the surrounding tissues, resulting in an overdose of the patient. Slicing the catheter may also necessitate a replacement, prolonging the procedure.

2. Open the pump pocket.

   Warning: Use a barrier to prevent Remodulin from leaking into the subcutaneous tissue. Remodulin leaking into the subcutaneous tissue may cause an overdose of the patient.

3. Remove the old pump from the pump pocket.

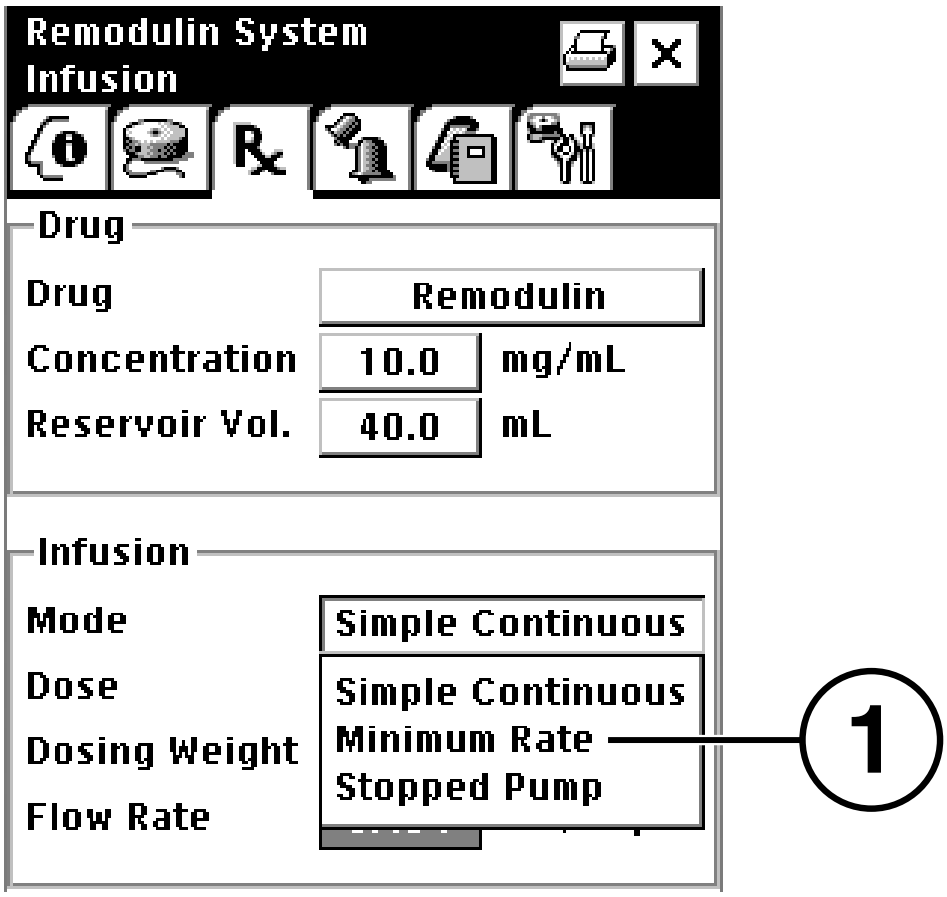
14.7.2 Programming the old pump to Minimum Rate

To program the pump to Minimum Rate, complete the following steps:

1. Interrogate the pump.
2. Select the Infusion screen tab.

3. Select Minimum Rate from the Infusion Mode drop-down list (see Figure 77).

Figure 77. Minimum Rate



4. Read the warning and select the Yes button to set the pump to Minimum Rate.
5. Update the pump (see Section 9.3).

14.7.3 Disconnect the old pump

1. Disconnect the sutureless connector from the pump.
   a. Pinch the black dots on the sutureless connector and disconnect the sutureless connector from the pump.
   b. Use gauze to catch any liquid that may leak out from the pump or the catheter.
   c. Verify that no fluid drips from the catheter or pump into the tissue of the patient.
2. Dispose of the old pump. See the instructions in Section 17.1.

14.8 Connecting the new pump

Warnings:

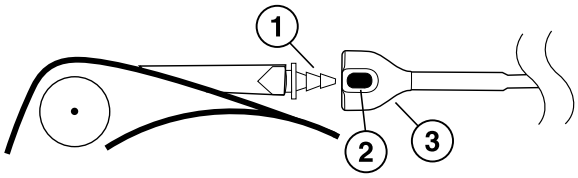
- If this is a pump replacement and the catheter has not been replaced, prime the pump tubing and flush the catheter access port before connecting the catheter and the pump. Do not program a postoperative priming bolus after connecting the catheter and the pump. Programming a postoperative priming bolus after connecting the catheter and the pump can result in a clinically significant or fatal overdose of Remodulin.
- Do not flush the catheter access port with Remodulin after it is connected to the catheter. Flushing the catheter access port with the catheter connected can result in a clinically significant or fatal overdose of Remodulin.

Warning: Do not connect the catheter to the pump until the prime and catheter access port flush have been completed. Doing so may result in an overdose of the patient.

Warning: Verify that the catheter is not damaged during explant and that the sutureless connector is secured correctly to the catheter. Damage to the catheter or an incomplete connection to the sutureless connector may result in Remodulin leaking into the surrounding tissue, which may cause a localized tissue reaction or reduced drug therapy.

1. Connect the sutureless connector to the pump by pinching the black oval dots on the proximal end of the sutureless connector (see Figure 78).

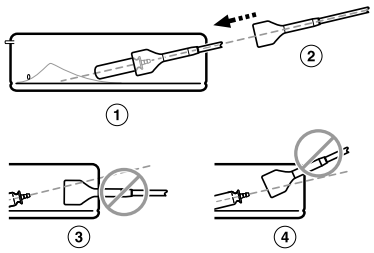
Figure 78. Connecting the sutureless connector to the pump



1 Catheter port on the pump
2 Oval on the sutureless connector
3 Tapered portion of the sutureless connector

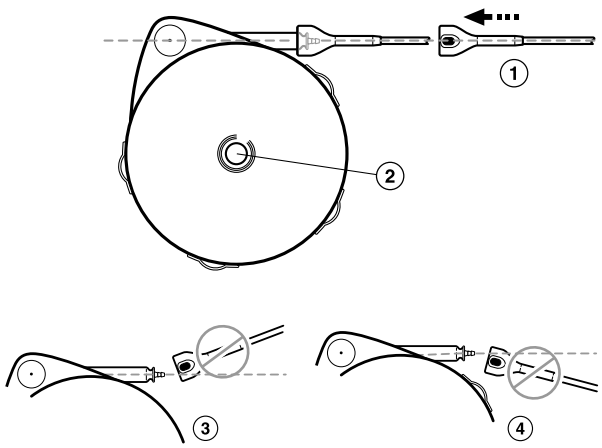
2. Examine Figure 79 and Figure 80. These figures depict correct alignment and incorrect alignment of the sutureless connector to the pump.

Figure 79. Connector — correct and incorrect alignment



1 Catheter port on this side
2 Correct alignment
3 Incorrect alignment
4 Incorrect alignment

Figure 80. Pump view — correct and incorrect alignment



1 Correct alignment
2 Reservoir fill port
3 Incorrect alignment
4 Incorrect alignment

3. Check for proper connection by tugging (Figure 81) and freely rotating (Figure 82) the sutureless connector on the pump.

Figure 81. Tug to check for proper connection

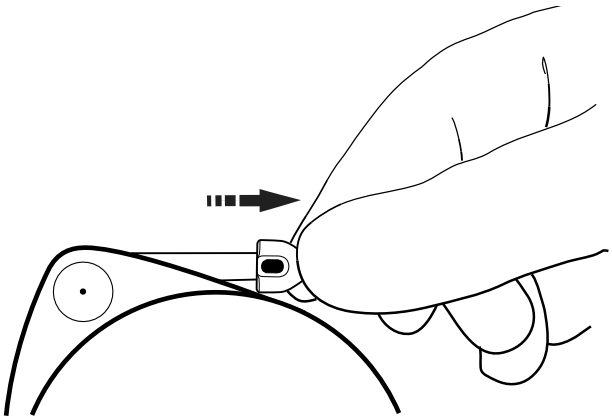
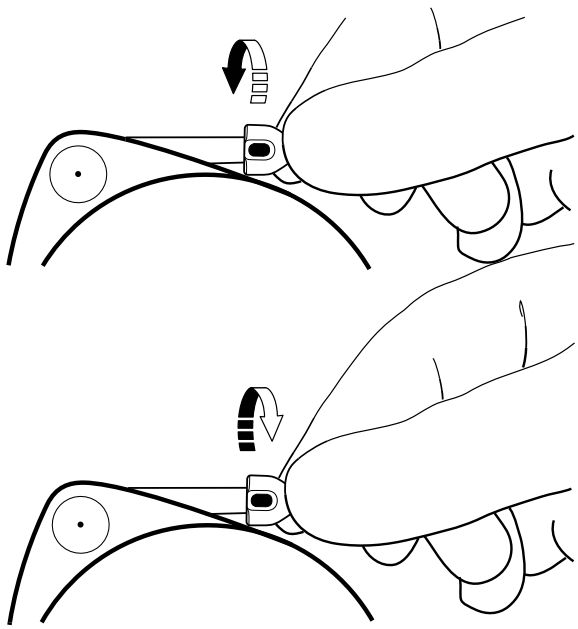


Figure 82. Rotate to check for proper connection



14.9 Programming the new pump to Simple Continuous mode

14.9.1 Programming the new pump to Simple Continuous mode

To program the new pump to Simple Continuous mode, perform the following steps:

1. Pass the programming head into the sterile field with the programming head inside a sterile sleeve. If the programmer was shut off, turn the programmer back on and re-interrogate the pump.
2. Select the Infusion screen tab.

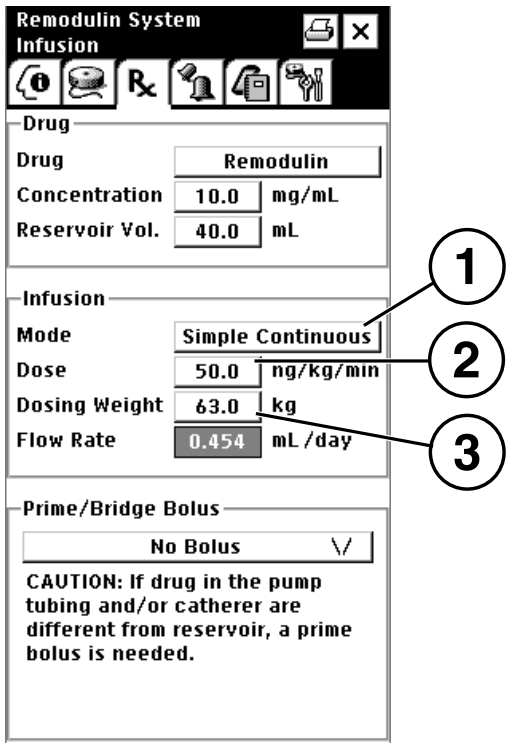
3. Select the Mode button and change the mode to Simple Continuous from the drop-down list.

   Warning: Confirm that the intended drug dosage is selected and programmed. Selecting and programming an incorrect drug dosage may lead to a potential drug overdose or underdose of the patient.

4. Select the Dose button and put in the appropriate dose of Remodulin.
5. Select the Dosing Weight button and put in the appropriate dosing weight (see Figure 83).

   Note: If using an external line, turn it off prior to updating the new pump to simple continuous.

Figure 83. Simple Continuous Mode



1 Mode is set to Simple Continuous
2 Dose of Remodulin
3 Dosing Weight

6. Update the pump (see Section 9.3).

14.9.1.1 Administration

Warning: Verify that the scheduled refill date is on or before the Low Reservoir Alarm date. An incorrect refill date may cause the alarm to sound and underdosing of the patient to occur.

1. Print out the patient's prescription and pump settings (pump status).
2. Place the prescription and pump settings into the patient's records.
3. Determine the refill date from the printout.
4. Schedule a refill appointment.
5. Observe the patient for a minimum of 1 hour following a pump refill.

14.10 Implant the new pump

Cautions:

- Implant the pump no more than 2.5 cm from the surface of the skin to maintain access to the reservoir and catheter access ports.
- Place the pump in the prepared pocket so that the reservoir fill port is anteriorly oriented and the reservoir fill port and the catheter access port are easy to access after implant.
- Place the pump so that no sutures to the skin are directly over the reservoir fill port or the catheter access port.

Improper component placement can result in inaccessible pump ports, inadequate drug delivery, component damage, or procedural delays, and may require surgical revision or replacement.

1. Place the filled pump into the prepared pocket.

   Cautions:

   - Secure the catheter body well away from the pump ports.
   - Place the sutureless connector on the outside of the pump perimeter with the excess catheter body wrapped underneath the pump. Do not kink or twist the excess catheter body.
   - Place the sutureless connector outside of the pump's suture loops before suturing the pump.

2. Place the excess catheter body into the pump pocket:
    a. Ensure that the sutureless connector and its connection are wrapped outside of the pump perimeter away from the pump's suture anchor sites, and that the sutureless connector is still visible under fluoroscopy.
    b. Wrap any excess catheter body behind the pump.
3. Suture the pump in the subcutaneous pocket using the following steps:
    a. Suture the first 2 suture loops to the fascia in the bottom of the subcutaneous pocket.
    b. Use these 2 sutures and the lower suture loops on the pump to draw the pump into the pocket.
    c. Tie the sutures.
    d. Suture the remaining 2 loops at the top of the pump pocket.
    e. Tie the sutures, securing the pump into the pocket.
4. Irrigate the pump pocket.
5. Close the incisions per normal procedure and apply dressing.

15 Catheter replacement

15.1 Assembling system components for a new catheter implant

Assemble the following components:

- Model 8201 Implantable Intravascular Catheter
- introducer kit (8 Fr) and, if using valved introducer kit, 1 transvalvular introducer tool
- tunneling catheter passer
- N'Vision Model 8840 Clinician Programmer with the Model 8870 Application Card

15.2 Explanting the old catheter

Warnings:

- Prior to catheter replacement, verify that the implanted pump is set to Minimum Rate. If the pump is not set to Minimum Rate, excess Remodulin® (treprostinil) Injection could leak from the pump into the subcutaneous tissue and cause an overdose of the patient.
- Before replacing the catheter, verify that Remodulin is being delivered to the patient by an external line. If Remodulin is not being delivered by an external line during a catheter replacement, the patient may be underdosed. All procedures where an external line is used to provide supplemental therapy require that the implanted pump be first reprogrammed to the Minimum Rate for infusion before beginning supplemental therapy. Failure to do so may result in a clinically significant drug overdose including hemodynamic collapse or death.

To remove the old catheter, perform the following steps:

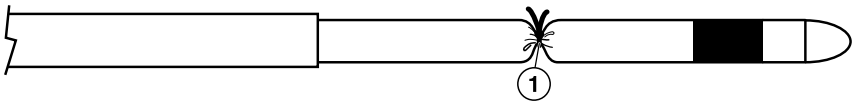
1. Use fluoroscopy to view the catheter implant pathway to avoid cutting the catheter during explant.

   Caution: Do not cut or puncture the catheter or invert the sleeve valve. This may allow Remodulin to leak into subcutaneous tissue and cause a potential overdose of the patient.

2. Open the venous access site.
3. Remove any sutures from the anchoring sleeve and the retention sleeve, if used, from the tissue.
4. Use gentle traction to remove the catheter from the vasculature.

5. Tie a suture tightly around the catheter body near the sleeve valve to fully occlude the catheter and minimize leakage of the drug (see Figure 84).

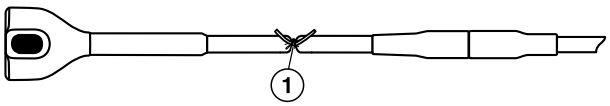
Figure 84. Catheter occluded



1 Suture tied to occlude catheter

6. Remove the anchoring sleeve from the catheter. Remove all remaining sutures from the anchoring sleeve and the retention sleeve (if used). Remove the anchoring sleeve and the retention sleeve (if used) by sliding the anchoring sleeve completely off the distal end (the sleeve valve) of the catheter.
7. Open the pump pocket.
8. Tie a suture or put a clamp around the sutureless connector body to minimize leakage of the drug from the catheter (see Figure 85).

Figure 85. Sutureless connector occluded



1 Suture tied to occlude sutureless connector

9. Free the catheter from the pump pocket.
10. Disconnect the sutureless connector from the pump by performing the following steps:
    a. Pinch the black oval dots on the sutureless pump connector and slide the sutureless connector off of the catheter port on the pump.
    b. Use gauze to catch any drug that may leak out from the pump or catheter.
    c. Verify that no fluid drips from the catheter or pump into the tissue of the patient.
11. Remove the catheter from the subcutaneous pathway by pulling it into the pump pocket.
12. Dispose of the old catheter. See the instructions in Section 17.1.

15.3 Preparing the new catheter for implant

Warning: Use of catheters may cause trauma to the heart and vasculature. Do not apply force to the catheter during the implant procedure if significant resistance is encountered. Applying force may injure the patient.

Cautions:

- Handle the catheter with care at all times. Do not use the catheter if it has been damaged. A damaged catheter may allow blood to enter the catheter valve and occlude the catheter, resulting in a reduced or an abrupt cessation of drug delivery.
- Before implanting the catheter, determine if the catheter length is suitable for the patient's body size. A catheter that is too short may result in dislodgement of the catheter from the vasculature or may cause patient discomfort because of insufficient strain relief. A catheter that is too long may result in difficulty wrapping the excess length and securing it under the pump. Do not cut the catheter to size for the patient.
- When preparing the catheter for implant, do not connect the sutureless connector to the catheter until instructed to do so.
- Do not use a needle to flush the catheter. The needle may puncture the catheter, allowing drug to leak into the surrounding tissue when the catheter is implanted. Leakage may result in a site reaction or a drug underdose.
- Do not wipe the distal tip of the catheter with gauze or with your fingertips. Damage may occur. Do not touch or contact the one-way valve. Doing so may cause an inversion of the one-way valve, which may lead to a catheter occlusion and an abrupt cessation of drug delivery.
- If the catheter cannot be successfully flushed, select a new catheter and repeat the steps in this section. An occluded catheter may result in a loss of or a change in therapy, which may lead to a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug underdose.

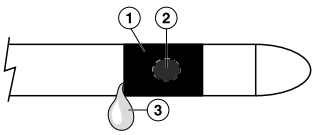
Flush the catheter with sterile saline solution before implanting the system. To flush the catheter, perform the following steps:

Caution: Slowly inject the sterile saline solution into the catheter. Injecting the sterile saline solution too quickly or with too much force can damage the catheter. A damaged catheter may allow blood to enter the catheter valve and occlude the catheter, resulting in a reduced or an abrupt cessation of drug delivery.

1. Flush the catheter with a 3 mL syringe filled with sterile saline solution. Apply light pressure to the syringe plunger until the sterile saline solution drips from the sleeve valve.

2. Visually observe that the sterile saline solution drips from the sleeve valve (see Figure 86).

Figure 86. Sleeve valve covering the side hole of the catheter



1 Sleeve valve
2 Side hole
3 Sterile saline solution dripping from the sleeve valve

3. Visually examine the distal tip of the catheter for damage. Verify that the sleeve valve is intact and that it covers the side hole.

15.4 Implanting the new catheter

15.4.1 Select an introducer delivery system

Cautions:

- Use an 8 Fr introducer without a retained guide wire. Use of an introducer with a retained guide wire can damage the catheter.
- If a valved introducer is used, a 9 Fr transvalvular introducer tool must be used to prevent damage to the catheter.

Use a compatible introducer delivery system to implant the catheter. A compatible introducer delivery system includes an 8 Fr introducer that is peelable, splittable, or slittable. The 8 Fr introducer may or may not include a hemostasis valve.

15.4.2 Gain venous access

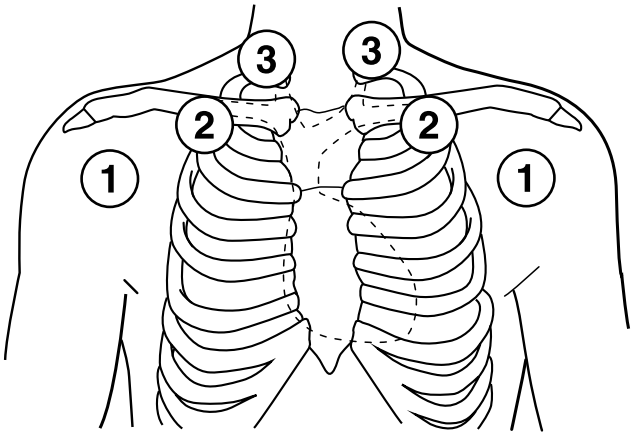
Cautions:

- When using a subclavian approach for catheter insertion, use a more lateral approach to minimize the risk of first rib clavicular crush. First rib clavicular crush may subsequently fracture the body of the catheter.
- Certain anatomical abnormalities, such as thoracic outlet syndrome, may pinch and subsequently fracture the catheter.

Select a venous insertion site for the catheter based on the planned vascular path. See Figure 87 for the suggested insertion sites.

Note: The cephalic cutdown method is recommended to minimize risk of pneumothorax.

Figure 87. Suggested insertion sites for the catheter



1 Cephalic cutdown
2 Subclavian or axillary stick
3 Jugular

15.4.3 Insert the catheter into the vein

Warning: Do not force the catheter through the vasculature if significant resistance is encountered during passage of the catheter. Applying excessive force may injure the patient's vasculature or heart, or the catheter.

Use caution when inserting the catheter into the vein:

- Do not severely bend, kink, or stretch the catheter.
- Do not use surgical instruments to grasp any part of the catheter.
- Do not insert any tool into the lumen of the catheter, such as a wire or a stylet.

Insert the catheter through the introducer into the vein.

To insert the catheter into the vein, perform the following steps:

1. Insert a compatible introducer into the vein.

   Note: Use the vein pick, as necessary, to gain access to the chosen vein.

2. Advance the catheter via the introducer into the superior vena cava (SVC). See the introducer product literature for additional information on the use of the introducer.
3. Advance the catheter through the vasculature into the SVC.

   Note: If venous tortuosity prevents advancement of the catheter tip into the SVC, a longer or kink-resistant introducer may be used.

4. Remove the introducer from the catheter and vasculature.

15.4.4 Avoid damage to the sleeve valve or distal tip of the catheter

Use caution to avoid damage to the distal tip of the catheter after it is inserted through the introducer.

Caution: The catheter sleeve valve may be damaged if the catheter tip is pulled back through the introducer.

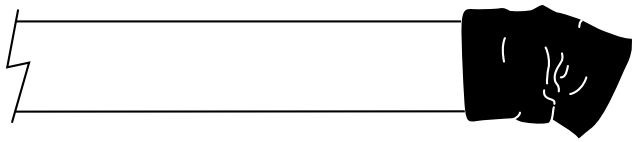
If the catheter must be pulled back through the introducer, slowly pull the catheter completely out of the introducer and then inspect the catheter sleeve valve for damage. Damage can include, but is not limited to, a torn catheter sleeve valve or an inverted catheter sleeve valve.

See Figure 88 for an example of a torn catheter sleeve valve.

Figure 88. Torn catheter sleeve valve

See Figure 89 for an example of an inverted catheter sleeve valve.

Figure 89. Inverted sleeve valve



15.4.5 Position the tip of the catheter

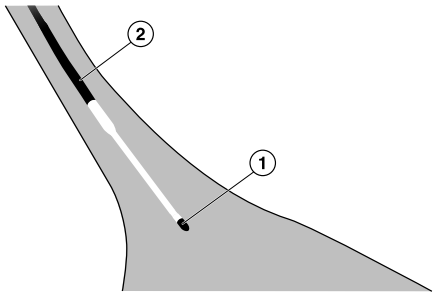
When positioning the tip of the catheter during implant, use caution to ensure that the catheter tip is not wedged against the vasculature or the heart wall. Allow the tip to free-float in the superior vena cava (SVC).

Warning: Do not advance the catheter into the right atrium or atrial fibrillation may occur.

To position the tip of the catheter, perform the following steps:

1. Advance the distal tip of the catheter to the SVC-atrial confluence just outside the right atrium.
2. Position the anchoring sleeve at the venous access site.
3. Use fluoroscopy to verify the location of the distal tip of the catheter at the SVC-atrial confluence (see Figure 90). Verify that the distal tip is not in contact with the vessel wall.

Figure 90. Implanted catheter under fluoroscopy



1 Distal tip of the catheter under fluoroscopy
2 Catheter body under fluoroscopy

Note: The distal tip of the catheter has an enhanced radiopaque marker band to aid in catheter tip placement under fluoroscopy.

15.4.6 Anchor the catheter

Caution: Verify that the catheter is anchored properly. Improper or incomplete anchoring may result in catheter dislodgement from the vasculature or catheter occlusion.

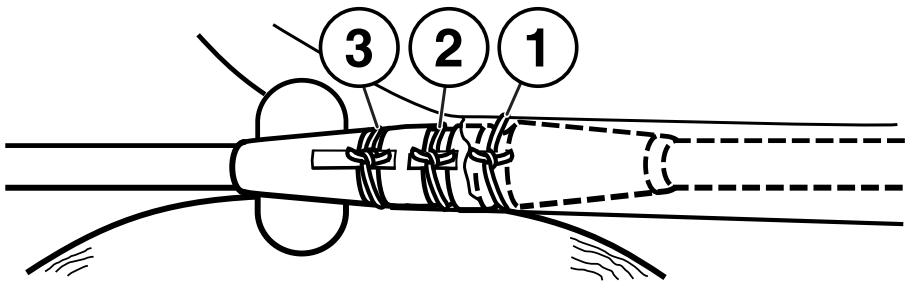
The anchoring sleeve is used to secure the catheter to muscle or fascia with sutures. When securing the anchoring sleeve:

- Do not tie a suture directly onto the catheter body. Tie the sutures to the anchoring sleeve.
- Do not attempt to remove or alter the anchoring sleeve.
- Do not move the catheter while suturing.
- Do not use absorbable suture ties.
- Do not occlude the catheter lumen by tying the sutures too tightly.
- Do not use the anchoring sleeve tabs for suturing.

To anchor the catheter, perform the following steps:

1. Secure suture groove 1 of the anchoring sleeve to the vein, if needed for hemostasis, with a non-absorbable suture (see Figure 91).
2. Secure the anchoring sleeve to the catheter with 2 suture ligatures tied tightly enough to slightly indent the catheter coils. Use the second and third grooves to secure anchoring sleeve to the catheter body only (see Figure 91). Do not secure the anchoring sleeve to tissue.

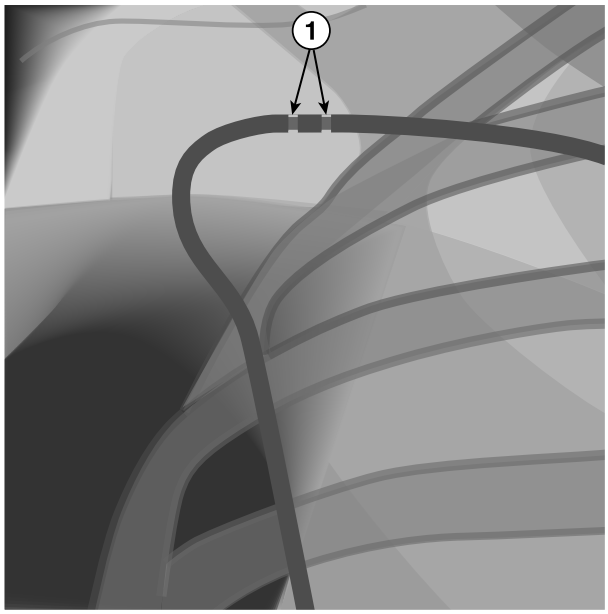
Figure 91. Secure the anchoring sleeve to the vein and the catheter body



1 Suture secured around the vein
2 Suture secured to the anchoring sleeve only
3 Suture secured to the anchoring sleeve only

3. Use fluoroscopy to verify that the coil beneath the sutures is indented. If the coil is not indented, tie the anchoring sleeve again. Visual indents ensure that the compressive force is adequate. The indents appear as reduced radiopacity of the catheter body (see Figure 92).

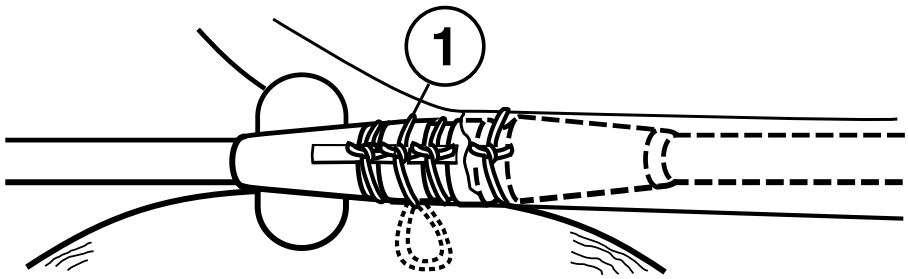
Figure 92. Verify that the coil beneath the sutures is indented[3]



1 Two indents on the catheter body

4. Secure the anchoring sleeve to fascia with one or more sutures tied through tissue and around the anchoring sleeve (see Figure 93).

Figure 93. Securing the anchoring sleeve to fascia



1 Suture tied around the anchoring sleeve and secured to fascia or tissue

[3] Do not rely on the fluoroscopy image for determination of adequate sutures. The fluoroscopy image has not been validated.

5. Use the retention sleeve if additional sutures are needed for the catheter.
6. Verify under fluoroscopy that the catheter tip is still positioned as intended.

15.5 Tunneling the new catheter

Prior to tunneling the catheter, select a compatible tunneling tool that allows passage of a catheter, including the catheter connection (see Section 3.4.3 for the catheter dimensions). Refer to the applicable instructions for use for the tunneling tool.

Caution: Use caution when performing the tunneling procedure to prevent the tunneling tool from perforating the diaphragm or internal organs.

To tunnel the catheter, perform the following steps:

1. Tunnel subcutaneously between the venous access site and the pump pocket site with a tunneling catheter passer.

   Note: If you tunnel starting at the venous access site to the pump pocket, use a tunneling tool with a removable handle. Remove the obturator from the tunneling tool handle after tunneling is completed. Remove the tunneling tool handle from the tunneling tool.

2. Insert the catheter directly into the open lumen of the tunneling tool shaft.

   Caution: Use caution when passing the catheter to the pump pocket site. The catheter can be dislodged or damaged if it is handled roughly.

3. Pass the catheter from the venous access site to the pump pocket site.
4. Hold the catheter at the venous access site while removing the tunneling tool. Slowly remove the tunneling tool from the tunneling path through the abdominal pocket site.
5. Adjust the catheter slack between the venous access site and the pump pocket site. Ensure that sufficient catheter slack is present at the venous access site.

15.6 Attaching the new catheter to the old pump

15.6.1 Attach the new catheter to the new sutureless connector

Warning: Do not perform a system integrity check or flush any fluid into the catheter access port. Remodulin is in the catheter access port, and a system integrity check or a fluid flush of the catheter access port may deliver an excess of Remodulin to the patient. This action may cause a life-threatening overdose of the patient.

Warning: Verify that the catheter is not damaged during explant and that the sutureless connector is secured correctly to the catheter. Damage to the catheter or an incomplete connection to the sutureless connector may result in Remodulin leaking into the surrounding tissue, which may cause a localized tissue reaction or reduced drug therapy.

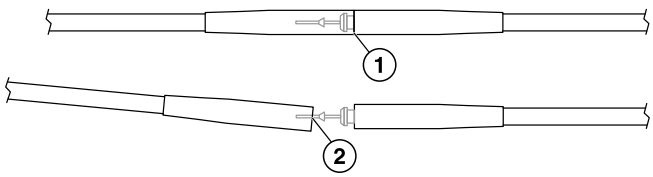
Caution: Ensure that blood does not enter the lumen of the new sutureless connector or the catheter. Blood ingression into the catheter may result in a catheter occlusion and an underdose of the patient.

To attach the catheter to the sutureless connector, perform the following steps:

1. Align the sutureless connector pin with the lumen of the catheter.
2. Insert the sutureless connector pin straight into the lumen of the catheter.
3. Ensure that there is no gap between the connection of the proximal end of the catheter connector and the sutureless connector.

   Figure 94 shows correct and incorrect insertion of the sutureless connector pin.

   Figure 94. Sutureless connector pin inserted correctly and incorrectly into the lumen of the catheter

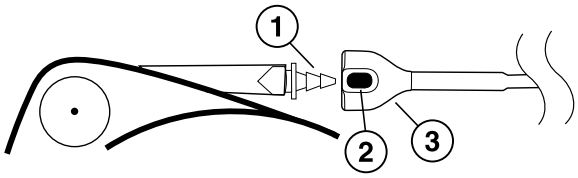


1 Sutureless connector pin inserted correctly into the lumen of the catheter
2 Sutureless connector pin inserted incorrectly into the lumen of the catheter

15.6.2 Attach the new sutureless connector to the old pump

1. Connect the sutureless connector to the pump by pinching the black oval dots on the proximal end of the sutureless connector (see Figure 95).

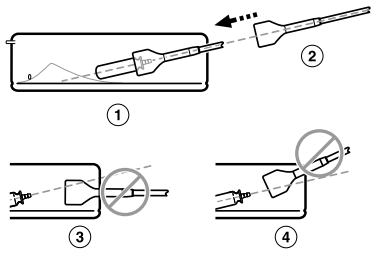
Figure 95. Connecting the sutureless connector to the pump



1 Catheter port on the pump
2 Oval on the sutureless connector
3 Tapered portion of the sutureless connector

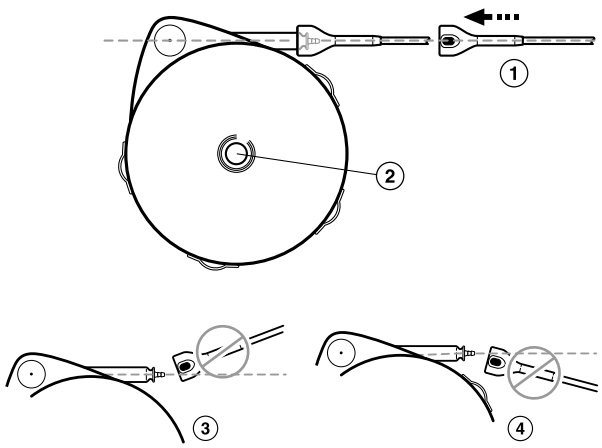
2. Examine Figure 96 and Figure 97. These figures depict correct alignment and incorrect alignment of the sutureless connector to the pump.

Figure 96. Connector — correct and incorrect alignment



1 Catheter port on this side
2 Correct alignment
3 Incorrect alignment
4 Incorrect alignment

Figure 97. Pump view — correct and incorrect alignment



1 Correct alignment
2 Reservoir fill port
3 Incorrect alignment
4 Incorrect alignment

3. Check for proper connection by tugging (Figure 98) and freely rotating (Figure 99) the sutureless connector on the pump.

Figure 98. Tug to check for proper connection

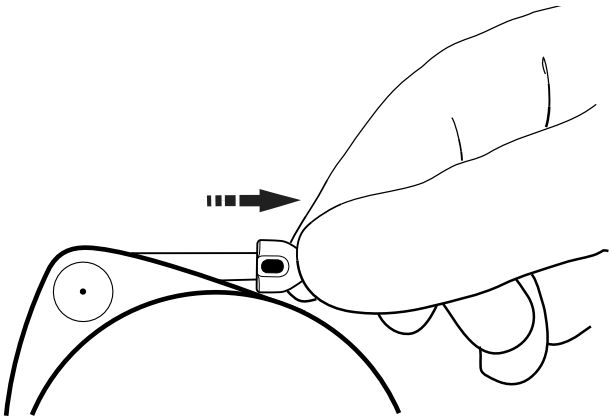
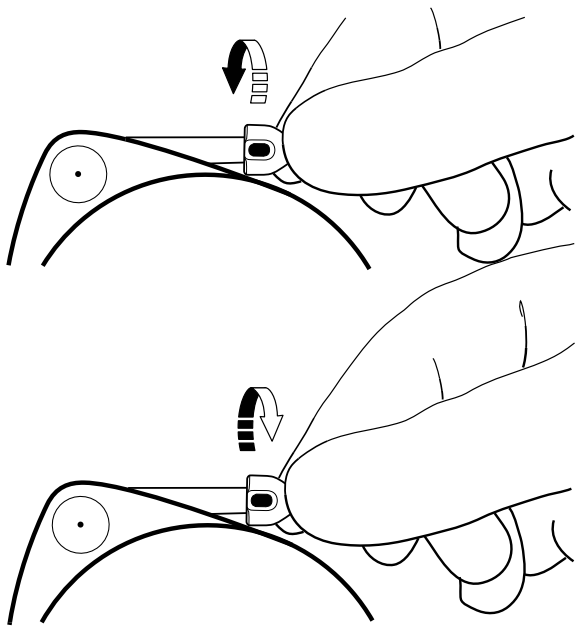


Figure 99. Rotate to check for proper connection



Cautions:

- Wrap the catheter body so as not to kink or twist the excess catheter body.
- Secure the catheter body well away from the pump ports.
- Place the sutureless connector outside of the pump's suture loops before suturing the pump.

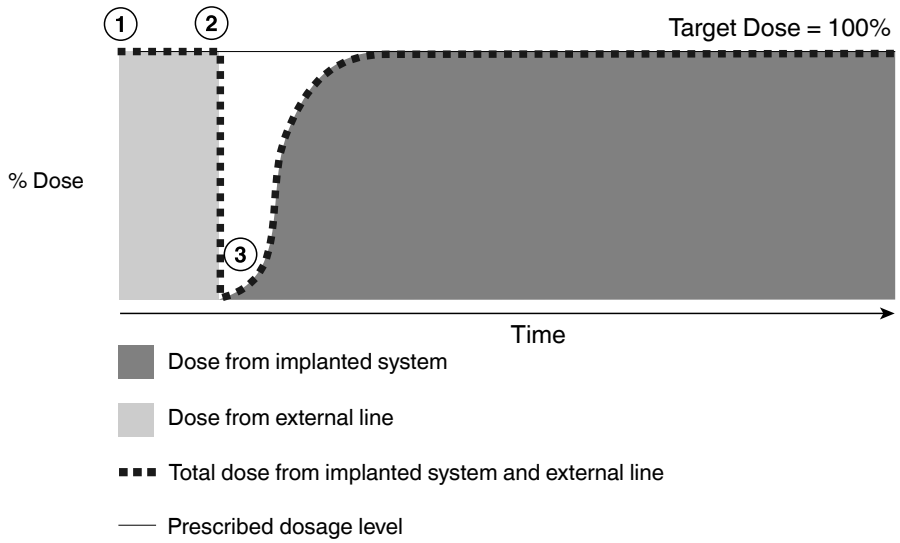
4. Place the excess catheter body into the pump pocket:
   - Ensure that the sutureless connector and its connection are wrapped outside of the pump perimeter away from the pump's suture anchor sites, and that the sutureless connector is still visible under fluoroscopy.
   - Wrap any excess catheter body behind the pump.
5. Irrigate the pump pocket.
6. Close the incisions per normal procedures and apply dressing.

15.7 Prime for Catheter Replacement overview

Prime for Catheter Replacement is performed for a catheter-only replacement. The pump remains implanted and is filled with Remodulin. Before you perform the Prime for Catheter Replacement, verify that Remodulin is being delivered through an external line.

The typical dosing profile for Prime for Catheter Replacement, including the dose delivered by the external line, is shown in Figure 100.

Figure 100. Typical dosing profile of a prime for catheter replacement



1 Prime Bolus start = 100% dose from external line + 0% dose from implanted system
2 Prime ends = 100% dose from external line + 0% dose from implanted system
3 External line turned off = 0% dose from external line + implanted system reaches 100% dose very quickly

The mixing of drug and sterile saline in the catheter is minimal. The concentration of the drug quickly increases after the Prime for Catheter Replacement ends.

When the Prime for Catheter Replacement ends, stop the flow of Remodulin through the external line. See Table 11 for the default Prime for Catheter Replacement durations for each Model 8201 catheter length.

Table 11. Default Prime for Catheter Replacement parameters

Catheter model number and length (in cm)	Default Prime for Catheter Replacement duration (in min)
8201-80	10

15.8 Programming the Prime for Catheter Replacement

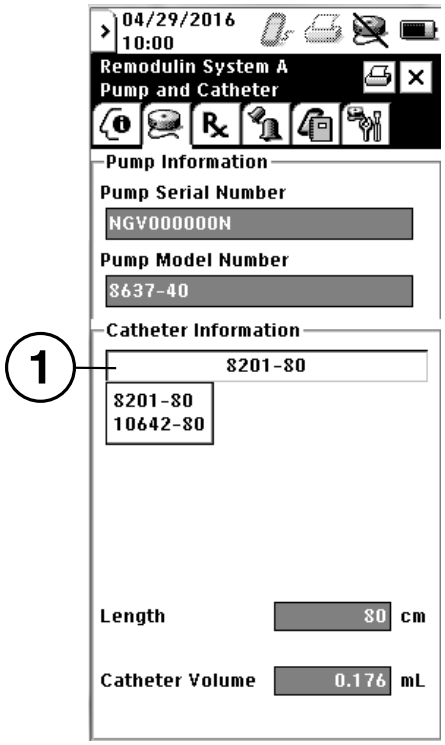
Warnings:

- Conduct the Prime for Catheter Replacement procedure under supervision of a PAH clinician. An overdose or underdose of the patient may occur and may require medical management of the patient.
- Confirm that the intended catheter is selected and programmed. Selecting and programming an incorrect catheter model number may lead to a potential drug overdose or underdose of the patient.

1. Interrogate the pump.
2. Update the catheter model, if applicable.
   a. Select the Pump and Catheter screen tab.

   b. Select the catheter model from the drop-down list (see Figure 101).

Figure 101. Catheter Information

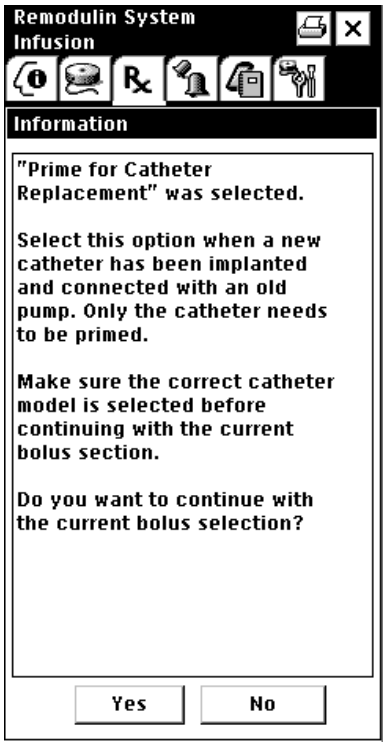


1 Field showing catheter selected

3. Select the Infusion screen tab.

4. Select the Mode button and select Simple Continuous from the drop-down list.
5. Confirm that the dose and the dosing weight are correct for this patient.
6. Select the Prime Bolus button.
7. Select Prime for Catheter Replacement from the drop-down list.
8. Read the Information screen and select Yes (see Figure 102).

Figure 102. Prime for Catheter Replacement Information



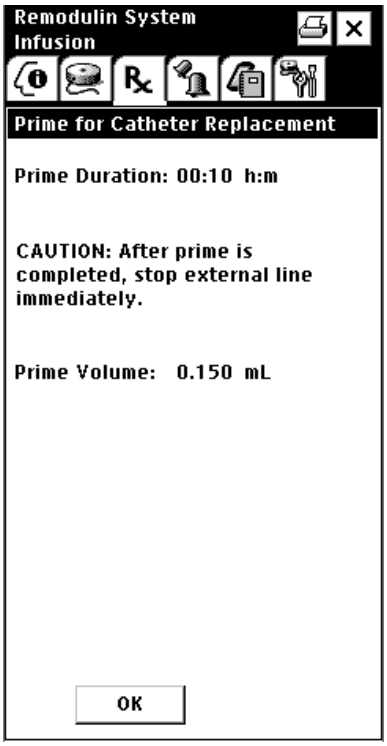
9. Select the Details button for more information about when to stop the external line after the bolus starts.

   Warning: Closely monitor the patient during the transition of Remodulin delivery from the external line to the implanted system. An overdose or underdose of the patient may occur and may require medical management of the patient. If signs of overdose occur, the external line may be turned off earlier than the calculated time provided by the programmer.

   a. Record time duration to stop external line.
   b. Record the start time of Prime for Catheter Replacement and when to stop the external line.

10. Select the OK button to close the Details window (see Figure 103).

Figure 103. Prime for Catheter Replacement details



11. Update the pump (see Section 9.3).
12. From the Pump Status screen (scroll to the bottom), record the Low Reservoir Alarm Date.
13. When the update is complete, start a timer to track when to stop the external line. Record the start time of the prime and when to stop the external line.
14. Stop the external line at the recorded time.

15.8.1 Administration

Warning: Verify that the scheduled refill date is on or before the Low Reservoir Alarm date. An incorrect refill date may cause the alarm to sound and underdosing of the patient to occur.

1. Print out the patient's prescription and current pump settings (pump status).
2. Place the prescription and pump settings into the patient's records.

3. Determine the refill date from the printout.
4. Schedule a refill appointment.

16 Sutureless connector replacement

16.1 Assembling system components for a sutureless connector replacement

When it is necessary to replace a sutureless connector, use the sutureless connector packaged with the Model 8201 Implantable Intravascular Catheter.

Assemble the following sterile and non-sterile components:

- sutureless connector
- N'Vision Model 8840 Clinician Programmer with the Model 8870 Application Card

Warning: Before explanting a sutureless connector, set the implanted pump to Minimum Rate. If the pump is not set to Minimum Rate, excess Remodulin® (treprostinil) Injection may leak from the pump into the subcutaneous tissue and cause an overdose of the patient.

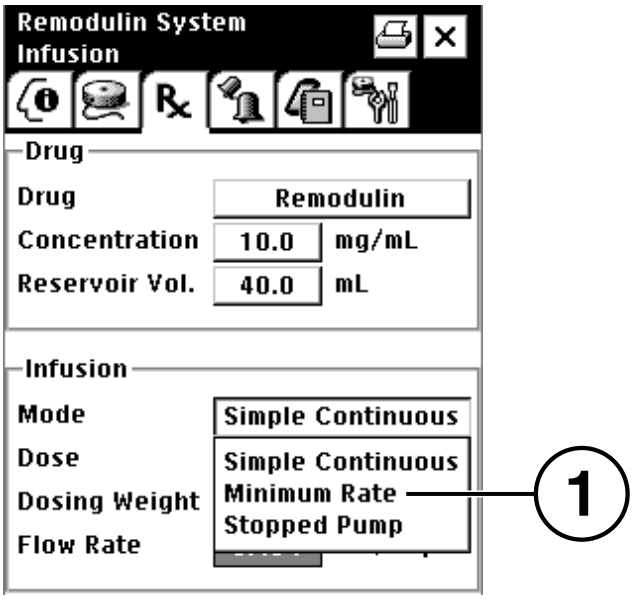
16.2 Programming the pump to Minimum Rate

To program the pump to Minimum Rate, complete the following steps:

1. Interrogate the pump.
2. Select the Infusion screen tab.

3. Select Minimum Rate from the Infusion Mode drop-down list (see Figure 104).

Figure 104. Minimum Rate



1 Minimum Rate is selected from the drop-down list

4. Read the warning and select the Yes button to set the pump to Minimum Rate.
5. Update the pump (see Section 9.3).

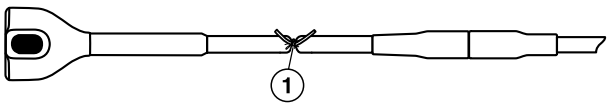
16.3 Explanting the old sutureless connector

Warning: Use care when explanting the sutureless connector to prevent damage to the catheter. Inadvertently slicing the catheter may cause Remodulin to leak into the surrounding tissues, resulting in an overdose of the patient. Slicing the catheter may also necessitate a replacement, prolonging the procedure.

To explant the old sutureless connector, perform the following steps:

1. Use fluoroscopy to view the catheter in the pump pocket.
2. Open the pump pocket.
3. Tie a suture or put a clamp around the sutureless connector body to minimize leakage of the drug from the catheter (see Figure 105).

Figure 105. Sutureless connector occluded



1 Suture occluding the sutureless connector

Warning: Use a barrier to prevent Remodulin from exiting the sutureless connector or pump and leaking into the subcutaneous tissue, which may cause an overdose of the patient.

4. Disconnect the sutureless connector from the pump.
   a. Pinch the black dots on the sutureless connector and disconnect the sutureless connector from the pump.
   b. Use gauze to catch any Remodulin that may leak out from the pump or the catheter.
   c. Verify that no fluid drips from the catheter or pump into the tissue of the patient.
5. Remove the sutureless connector from the catheter.
6. Dispose of the old sutureless connector. See the instructions in Section 17.1.

16.4 Implanting the new sutureless connector

16.4.1 Attach the catheter to the new sutureless connector

Warning: Do not perform a system integrity check or flush any fluid into the catheter access port. Remodulin is in the catheter access port, and a system integrity check or a fluid flush of the catheter access port may deliver an excess of Remodulin to the patient. This action may cause a life-threatening overdose of the patient.

Warning: Verify that the catheter is not damaged during explant and that the sutureless connector is secured correctly to the catheter. Damage to the catheter or an incomplete connection to the sutureless connector may result in Remodulin leaking into the surrounding tissue, which may cause a localized tissue reaction or reduced drug therapy.

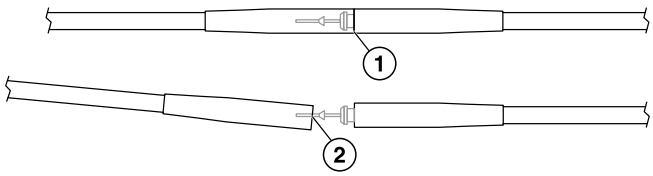
Caution: Ensure that blood does not enter the lumen of the new sutureless connector or the catheter. Blood ingression into the catheter may result in a catheter occlusion and an underdose of the patient.

To attach the catheter to the sutureless connector, perform the following steps:

1. Align the sutureless connector pin with the lumen of the catheter.
2. Insert the sutureless connector pin straight into the lumen of the catheter.
3. Ensure that there is no gap between the connection of the proximal end of the catheter connector and the sutureless connector.

   Figure 106 shows correct and incorrect insertion of the sutureless connector pin.

   Figure 106. Sutureless connector pin inserted correctly and incorrectly into the lumen of the catheter

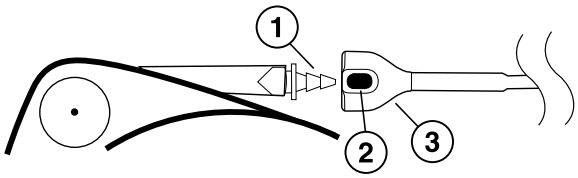


1 Sutureless connector pin inserted correctly into the lumen of the catheter
2 Sutureless connector pin inserted incorrectly into the lumen of the catheter

16.4.2 Connect the catheter with the new sutureless connector to the pump

1. Connect the sutureless connector to the pump by pinching the black oval dots on the proximal end of the sutureless connector (see Figure 107).

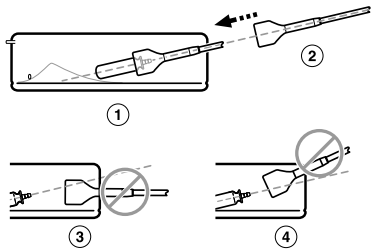
   Figure 107. Connecting the sutureless connector to the pump



1 Catheter port on the pump
2 Oval on the sutureless connector
3 Tapered portion of the sutureless connector

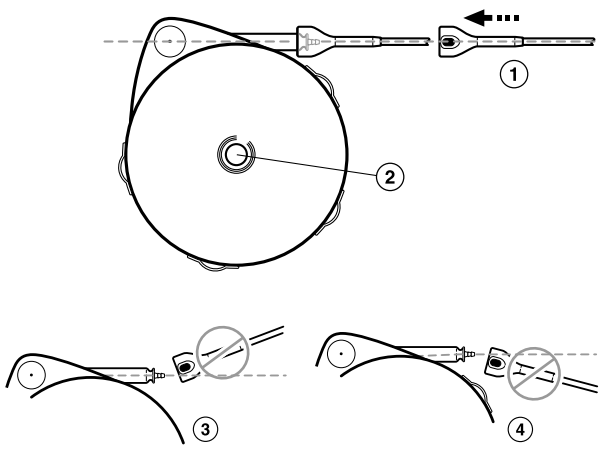
2. Examine Figure 108 and Figure 109. These figures depict correct alignment and incorrect alignment of the sutureless connector to the pump.

Figure 108. Connector — correct and incorrect alignment



1 Catheter port on this side
2 Correct alignment
3 Incorrect alignment
4 Incorrect alignment

Figure 109. Pump view — correct and incorrect alignment



1 Correct alignment
2 Reservoir fill port
3 Incorrect alignment
4 Incorrect alignment

3. Check for proper connection by tugging (Figure 110) and freely rotating (Figure 111) the sutureless connector on the pump.

Figure 110. Tug to check for proper connection

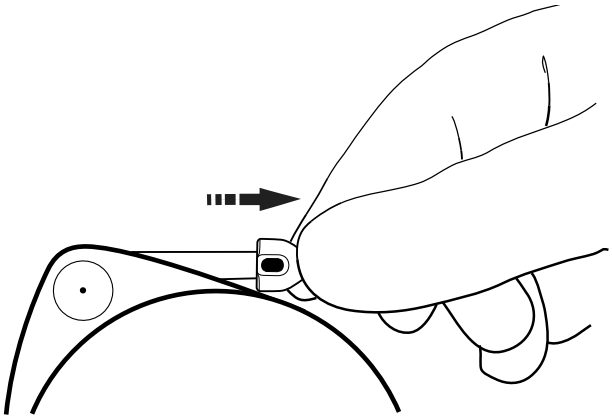
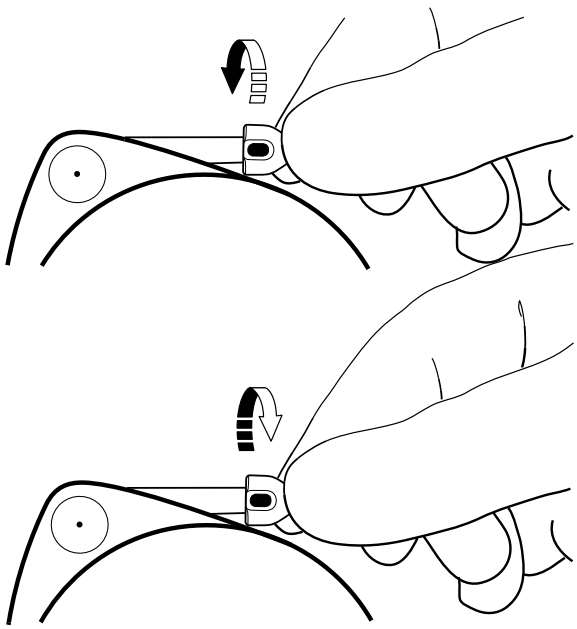


Figure 111. Rotate to check for proper connection



Cautions:

- Wrap the catheter body so as not to kink or twist the excess catheter body.
- Secure the catheter body well away from the pump ports.
- Place the sutureless connector outside of the pump's suture loops before suturing the pump.

4. Place the excess catheter body into the pump pocket:
   - Ensure that the sutureless connector and its connection are wrapped outside of the pump perimeter away from the pump's suture anchor sites, and that the sutureless connector is still visible under fluoroscopy.
   - Wrap any excess catheter body behind the pump.
5. Irrigate the pump pocket.
6. Close the incisions per normal procedures and apply dressing.

16.5 Programming the pump after replacing the sutureless connector

Warnings:

- Do not prime the system after the catheter is connected. Remodulin is in the catheter and a prime of the system could deliver an excess of Remodulin to the patient, potentially causing a life-threatening overdose.
- Verify that the Remodulin dose and dosing weight are set correctly for the patient. If the Remodulin dose or dosing weight are not set correctly for the patient, an underdose or overdose may occur.

To update the pump after replacing the sutureless connector, perform the following steps:

1. Interrogate the pump, if necessary.
2. Select the Infusion screen tab.

3. Select the Mode button and change the mode to Simple Continuous from the drop-down list.
4. Verify that the dose and dosing weight are set correctly for the patient.
5. Update the pump (see Section 9.3).

16.5.1 Administration

Warning: Verify that the scheduled refill date is on or before the Low Reservoir Alarm date. An incorrect refill date may cause the alarm to sound and underdosing of the patient to occur.

1. Print out the patient's prescription and current pump settings (pump status).
2. Place the prescription and pump settings into the patient's records.
3. Determine the refill date from the printout.
4. Schedule a refill appointment.

17 System component disposal

17.1 Disposing of system components

When explanting a component of the system (for example, replacement, cessation of therapy, or postmortem) or when disposing of components, follow these guidelines:

- Verify that the old pump is programmed to Minimum Rate before returning the pump to Medtronic.
- Return the explanted component with completed paperwork to Medtronic for analysis and disposal. See the back cover for the mailing address.
- To allow for component analysis, do not autoclave components or expose components to ultrasonic cleaners.
- Dispose of any unreturned components according to local environmental regulations; in some countries, explanting a battery-powered implantable pump is mandatory.
  - Do not incinerate or cremate the pump because it may explode if subjected to these temperatures.
  - Do not reuse any implantable component after exposure to body tissues or fluids because the functionality of the component cannot be guaranteed.

18 Electromagnetic Interference (EMI)

18.1 Introduction

Electromagnetic interference (EMI) is a field of energy generated by equipment found in the home, work, medical, or public environments that are strong enough to interfere with pump function. Programmable pumps include features that provide protection from electromagnetic interference. Most electrical devices and magnets encountered in a normal day are unlikely to affect the operation of a pump; however, sources of strong electromagnetic interference can result 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 overinfusion and a clinically significant or fatal drug overdose.

Caution: Advise the patient to seek medical guidance before entering an area marked with a warning notice prohibiting entry by patients with an implanted device. The operation of the infusion system can be adversely affected if the patient enters an area marked with a warning notice prohibiting entry by patients with an implanted device.

Before beginning any medical procedures, patients should always inform any health care personnel that they have an implanted infusion system and share this information about EMI with them. The potential for the following effects results from an interaction of the infusion system and equipment—even when both are working properly.

See Table 12 for information on sources of EMI, the effect of EMI on the patient and the infusion system, and instructions on how to reduce the risk from EMI.

For information about the effects of EMI on programming, see page 48.

For information about the effects of magnetic resonance imaging (MRI) on pump performance, see Section 6.3.

Table 12. Potential effects of EMI from devices or procedures

Device or procedure	Patient injury	System damage	Operational changes	Change in flow rate	For guidelines
Bone growth stimulators			X		page 183
Defibrillation/cardioversion		X			page 183
Diathermy	X			X	page 183
Electromagnetic field devices: (for example, arc welding, power stations)			X		page 183
High-output ultrasonics / lithotripsy		X			page 184
Laser procedures				X	page 184
Magnetic resonance imaging (MRI)	X	X	X	X	Chapter 19
Psychotherapeutic procedures			X	X	page 184
Radiation therapy		X			page 184
Radio-frequency (RF)/ microwave ablation			X	X	page 184
Theft detector			X		page 184
Therapeutic magnets			X		page 184

18.2 EMI warnings

EMI from the following medical procedures or equipment may damage system components, interfere with system operation, or cause harm to the patient. If these procedures are required, follow the guidelines below:

Diathermy – Avoid using shortwave (RF) diathermy within 30 cm of the pump or catheter. Energy from diathermy can produce a significant increase in temperature in the area of the pump and continue to heat the tissue in a localized area because the pump can retain heat. If overheated, a pump can overinfuse the drug, potentially causing a drug overdose. The effects of other types of diathermy (for example, microwave, ultrasound) on the pump are unknown.

Magnetic Resonance Imaging – See Chapter 19, “Magnetic resonance imaging (MRI)”, page 186.

18.3 EMI precautions

EMI from the following equipment is unlikely to affect the infusion system if the guidelines below are followed:

Bone growth stimulators – Keep external magnetic field bone growth stimulator coils 45 cm away from the infusion system.After using either an implantable or external bone growth stimulator,ensure the infusion system is working as intended.

Defibrillation or cardioversion – When a patient is in ventricular or atrial fibrillation, the first consideration is patient survival. Testing indicates defibrillation is unlikely to damage the pump; however, after defibrillation, confirm the pump is functioning as intended.

Electromagnetic field devices – Testing indicates that the pump motor will stop while exposed to magnetic fields of 57 gauss or more at a distance of 5 cm or less.Less powerful magnets at closer distances may also stop the pump.Magnetic fields of 10 gauss or less will generally not affect the pump. Patients should exercise care and avoid prolonged exposure to the following equipment or environments:

- Electric arc welding equipment
- High-voltage areas (safe if outside the fenced area)
- Magnets, degaussing equipment, or other equipment that generates strong magnetic fields
- Microwave communication transmitters (safe if outside the fenced area)
- Television and radio transmitting towers (safe if outside the fenced area)

If patients suspect that prolonged exposure to equipment is interfering with pump function, they should do the following:

1. Move away from the equipment or object.
2. If possible, turn off the equipment or object.
3. Inform the equipment owner or operator of the occurrence.

If the above actions do not resolve the effects of the interference, or the patients suspect that their therapy has been affected by exposure to electromagnetic interference (EMI), they should contact their physician.

High-output ultrasonics or lithotripsy – Use of high-output ultrasonic devices,such as electrohydraulic lithotriptors, is not recommended for patients who have an implanted pump. If lithotripsy must be used,do not focus the beam within 15 cm of the pump.

Laser procedures – Keep the laser directed away from the infusion system.

Psychotherapeutic procedures – Safety has not been established for psychotherapeutic procedures using equipment that generates electromagnetic interference, such as electroconvulsive therapy or transcranial magnetic stimulation, in patients who have an implanted infusion system. Induced electrical currents may cause heating of the pump,resulting in overinfusion and a clinically significant or fatal drug overdose.

Radiation therapy – Do not direct high radiation sources such as cobalt 60 or gamma radiation at the pump. If radiation therapy is required near the pump, place lead shielding over the pump to help prevent radiation damage.

Radio frequency or microwave ablation – Safety has not been established for radio frequency (RF) or microwave ablation in patients who have an implanted infusion system. Induced electrical currents may cause heating of the pump, resulting in overinfusion and a clinically significant or fatal drug overdose.

Theft detectors and security screening devices – When patients approach theft detector and security screening devices, such as those found in airports, libraries,and some department stores,they should not linger near or lean on the security screening device.

Therapeutic magnets, such as magnetic mattresses, blankets, wrist wraps, or elbow wraps – Keep the magnet at least 25 cm away from the pump. Magnetic fields of 10 gauss or less will generally not affect the pump.

18.3.1 EMI notes

Household items – Most household appliances and equipment, if working properly and grounded properly, will not interfere with the implanted infusion system.

Other medical procedures – Electromagnetic interference (EMI) from the following medical procedures is unlikely to affect the implanted infusion system:

- Computerized axial tomography (CT or CAT) scans

- Diagnostic ultrasound such as carotid scan or Doppler studies

  Note: To minimize potential image distortion, keep the transducer 15 cm away from the implanted infusion system.

- Diagnostic x-rays or fluoroscopy
- Electrocautery
- Magnetoencephalography (MEG)
- Positron emission tomography (PET) scans

19 Magnetic resonance imaging (MRI)

19.1 Introduction

Read this chapter before performing a magnetic resonance imaging (MRI) examination on a patient implanted with an Implantable System for Remodulin.

For further information or questions, contact Technical Services. For the number for Technical Services, see Section 2.4. Also review Table 12.

Proper patient monitoring must be provided during the MRI scan. This includes visual and verbal contact with the patient and monitoring heart rate using instrumentation such as pulse oximetry (plethysmography) or electrocardiography.

Before any medical procedure is begun, patients must always inform health care personnel that they have an implanted drug infusion system and share this information about MRI with them.

19.2 MRI information

Implantable System for Remodulin performance has been evaluated under certain conditions in both 1.5-Tesla (T) and 3 T horizontal cylindrical-bore MRI scanners. Implantable System for Remodulin performance has not been established using other types of MRI scanners such as open-sided or standing MRI.

19.2.1 Temporary motor stall and stall recovery

The magnetic field of the magnetic resonance imaging (MRI) scanner will temporarily stop the rotor of the SynchroMed II pump motor and suspend drug infusion for the duration of the MRI exposure. The pump should resume normal operation upon termination of MRI exposure; however, there is the potential for an extended delay in pump recovery after exiting the MRI magnetic field because exposure to the MRI magnetic field may cause the motor gears within the pump to bind temporarily without permanent damage. This is caused by the potential for backward rotation of the pump rotor magnet when it aligns with the MRI magnetic field. This temporary binding may delay the return of proper infusion after the pump is removed from the MRI magnetic field. While extended delays in pump recovery are unlikely, reports have indicated that there is the potential for a delay of 2 to 24 hours to return to proper drug infusion after completion of an MRI scan.

Warning: An abrupt cessation of Remodulin® (treprostinil) Injection can lead to life-threatening conditions if not treated promptly and effectively.

19.2.2 Time required for stall and recovery detection

The pump detects motor stall and motor stall recovery. Medtronic does not recommend programming the pump to “stopped pump mode” prior to a magnetic resonance imaging (MRI) because of the possibility of an increased delay in the detection of an extended motor stall.

Motor stall events are recorded in the pump event log and can be reviewed using the clinician programmer. A motor stall will also cause the pump alarm to sound (two-tone alarm). The slower the programmed delivery rate, the longer it may take for the stall detection algorithm to log motor stall and motor stall recovery. For pumps programmed to deliver at least 0.048 mL/day, the motor stall detection (with audible alarm) should occur within 20 minutes of exposure to the MRI magnetic field. Stall recovery detection should occur within 20 minutes of exiting the MRI magnetic field. The detection of a motor stall and detection of motor stall recovery may each take up to 90 minutes if the pump is programmed to minimum rate mode (0.006 mL/day).

19.2.3 Potential for delay in logging motor stall events

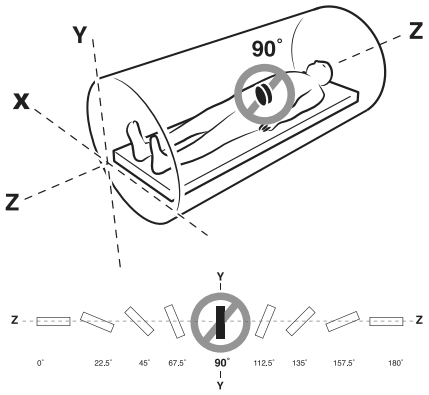
In some cases, electromagnetic interference (EMI) from an MRI scan can interfere with normal event logging. If this occurs, it may cause the pump to switch into the telemetry mode. “Telemetry mode” is a special state in which the pump is able to communicate with the clinician programmer. While in this state, the pump infuses normally; however, some error logging and the audible alarm for motor stall are suspended. If the pump switches into telemetry mode due to EMI, the pump resumes drug delivery after leaving the MRI magnetic field; however, pump motor stall and motor stall recovery detection function is not active until the post-MRI pump interrogation ends telemetry mode (see Section 19.2.6). Due to this issue, if the interrogation is not performed upon completion of the MRI scan or shortly thereafter, review of the pump logs may indicate that the pump ceased drug delivery for an extended period of time, when in fact it had recovered normally. In this scenario, you may receive an erroneous “stopped pump period may exceed tube set” error message.

Note: In some cases, the pump event log may not register motor stall recovery until after the pump has been interrogated a second time due to the effect of electromagnetic interference on the pump.

19.2.4 Potential for permanent motor stall

90° alignment of an implanted pump with the z axis (see Figure 112) of 1.5- T and 3.0- T horizontal, closed-bore magnetic resonance imaging (MRI) scanners can cause MRI induced demagnetization of the internal pump motor magnets, which can result in permanent, nonrecoverable stoppage of the pump. This is due to the orientation of the pump with respect to the magnetic field of a horizontal, closed-bore MRI system. The pump performance has not been established using other types of magnetic resonance imaging (MRI) scanners such as open-sided or standing MRI.

Figure 112. Pump positions in relation to z-axis MRI orientations



Note: If the pump face is oriented at 90° to the z-axis, the refill port would be facing towards the patient's feet or head.

19.2.5 Preparation for the MRI examination

Prior to magnetic resonance imaging (MRI), confirm the pump is not oriented 90° with respect to the z axis of the MRI scanner (see Figure 112). Also determine if the patient implanted with a SynchroMed II pump can safely be deprived of drug delivery. If the patient cannot be safely deprived of drug delivery, alternative delivery methods for the drug can be used during the time required for the MRI scan. If there is concern that depriving the patient of drug delivery may be unsafe for the patient during the MRI procedure, medical supervision should be provided while the MRI is conducted.

19.2.6 Post-MRI examination review

Warning: If the patient is receiving Remodulin through an external line, there is a risk of adverse events associated with overdose when the pump restarts. Remodulin overdose can lead to a life-threatening condition if not treated promptly and effectively.

Upon completion of the magnetic resonance imaging (MRI) scan, or shortly thereafter, confirm that therapy has properly resumed by interrogating the pump with the clinician programmer. For pumps programmed to deliver at least 0.048 mL/day, the detection of the motor stall should occur within 20 minutes of MRI exposure. Detection of the motor stall recovery and recording of the recovery in the pump event log will typically occur within 20 minutes of the removal of the pump from the MRI magnetic field.

Note: Both the detection of the motor stall and detection of the motor stall recovery may each take up to 90 minutes if the pump is programmed to minimum rate mode (0.006 mL/ day). In the unlikely event that electromagnetic interference from the MRI scan causes a change to “safe state”, the Implantable System for Remodulin in “safe state” continues to deliver drug at the previously programmed flow rate, if available. If the previously programmed flow rate is not available (corrupted), the pump will automatically switch to minimum rate mode (infusion at 0.006 mL/day). The pump must be reprogrammed to change the programmer from “safe state” to normal operating function.

The following pump interrogation guidelines should be used to determine whether the pump has resumed proper function. See Section 9.1 for information about how to interrogate the pump. See Section A.7 to view event logs.

1. At least 20 minutes after completing MRI exposure, interrogate the pump using the clinician programmer and select the check box to download event logs. If the event log states “Motor Stall Occurred” and “Motor Stall Recovery Occurred”, normal function of the pump has returned.
2. If the event log does not show stall and recovery, wait 20 minutes after the initial interrogation, reinterrogate the pump using the clinician programmer, and review the event logs again. (This will address the potential for event logging delays due to electromagnetic interference from the MRI magnetic field.)
3. If the motor stall has still not yet recovered, transport the patient to a care area where an external infusion system with the patient’s therapeutic dose of Remodulin is available. Interrogate the pump every 20 minutes and check for motor stall recovery.

4. If the pump has not recovered after 4 hours from the time the MRI scan was initiated, start the external infusion system with the patient's therapeutic dose of Remodulin. To ensure that the pump does not restart while the patient's external infusion pump is operating, update the pump infusion mode to Minimum Rate.
5. If the motor stall has not recovered at this point, call Technical Services (see Section 2.4).

19.2.7 Additional safety and diagnostic issues

Testing on the pump has established other magnetic resonance imaging (MRI) safety and diagnostic issues.

19.2.7.1 Tissue heating adjacent to implant during MRI scans

Specific absorption rate (SAR) – Presence of the pump can potentially cause an increase of the local temperature in tissues near the pump.

During a 20-minute pulse sequence in a 1.5- T GE Signa scanner with a whole-body average SAR of 1 W/kg, a temperature increase of 1°C in a static phantom was observed near the pump implanted in the "abdomen" of the phantom. The 20-minute scan time is representative of a typical imaging session. Implanting the pump more lateral to the midline of the abdomen may result in greater temperature increases in tissues near the pump.

Testing in a 3.0- T GE Signa scanner using transmit-receive RF body coil (at an MR system reported whole body averaged SAR of 3.0 W/kg and a spacial peak SAR of 5.9 W/kg) resulted in maximum heating of 2.7°C for the pump.

In the unlikely event that the patient experiences uncomfortable warmth near the pump, the MRI scan should be stopped and the scan parameters adjusted to reduce the SAR to comfortable levels.

19.2.7.2 Peripheral nerve stimulation during MRI scans

Time-varying gradient magnetic fields – Presence of the pump may potentially cause a two-fold increase of the induced electric field in tissues near the pump. With the pump implanted in the abdomen, using pulse sequences that have dB/dt up to 20 T/s, the measured induced electric field near the pump is below the threshold necessary to cause stimulation.

In the unlikely event that the patient reports stimulation during the scan, the proper procedure is the same as for patients without implants—stop the MRI scan and adjust the scan parameters to reduce the potential for nerve stimulation.

19.2.7.3 Static magnetic field

For magnetic fields up to 3.0 T, the magnetic force and torque on the pump will be less than the force and torque due to gravity. The patient may experience a slight tugging sensation at the pump implant site. An elastic garment or wrap will prevent the pump from moving and reduce the sensation the patient may experience.

19.2.7.4 Image distortion

The pump contains ferromagnetic components that will cause image distortion and image dropout in areas around the pump. The severity of image artifact is dependent on the MR pulse sequence used. For spin echo pulse sequences, the area of significant image artifact may be 20 to 25 cm across. Images of the head or lower extremities should be largely unaffected.

Note: Medtronic catheters have a non-magnetic metallic marker band at the tip which can also cause image artifact near the catheter tip and should be taken into consideration when evaluating images of this area.

Minimizing image distortion – Careful choice of pulse sequence parameters and location of the angle and location of the imaging plane may minimize MR image artifact; however, the reduction in image distortion obtained by adjustment of pulse sequence parameters will usually be at a cost in signal-to-noise ratio. The following general principles should be followed:

- Use imaging sequences with stronger gradients for both slice and read encoding directions. Employ higher bandwidth for both radio-frequency pulse and data sampling.
- Choose an orientation for read-out axis that minimizes the appearance of in-plane distortion.
- Use spin echo or gradient echo MR imaging sequences with a relatively high data sampling bandwidth.
- Use shorter echo time for gradient echo technique, whenever possible.
- Be aware that the actual imaging slice shape can be curved in space due to the presence of the field disturbance of the pump (as stated above).
- Identify the location of the implant in the patient, and when possible, orient all imaging slices away from the implanted pump.

A System troubleshooting

A.1 Catheter troubleshooting

A.1.1 Suspected local or subcutaneous delivery of Remodulin® (treprostinil) Injection

Caution: Do not perform a contrast dye test or inject dye or other fluid into the catheter access port. The catheter cannot be aspirated because of the one-way valve on the distal end. Injection of fluid into the catheter access port will result in an overdose.

Signs and symptoms of local or subcutaneous delivery of Remodulin include, but are not limited to, the following:

- pain or burning
- erythema
- induration
- rash

Local or subcutaneous Remodulin delivery could be due to, but not limited to, the following:

- leakage at junctions
- leakage at catheter break or hole in the catheter
- dislocation of the catheter from the vasculature

A.1.2 Suspected catheter occlusion

Caution: Medtronic recommends that a technical representative or subject matter expert be consulted or present while the patency procedure is performed.

Caution: Do not perform a contrast dye test or inject dye or other fluid into the catheter access port. The catheter cannot be aspirated because of the one-way valve on the distal end. Injection of fluid into the catheter access port will result in an overdose.

Catheter occlusion could result in signs and symptoms of Remodulin underdose related to returning or worsening pulmonary arterial hypertension and the lack of the patient's typical Remodulin side effects.

Returning or worsening pulmonary arterial hypertension symptoms include the following:

- dyspnea
- fatigue
- angina pectoris
- tachycardia
- pre-syncope
- edema
- hypoxia

The lack of the following typical side effects of Remodulin may also be characteristic of an abrupt cessation or a sudden large reduction of Remodulin:

- headache
- flushing
- diarrhea
- jaw or leg pain

Catheter occlusion could be due to, but is not limited to, the following:

- blood ingression into the catheter lumen
- fibrotic scar tissue encapsulating the catheter tip in the vasculature
- kink of the catheter lumen
- suture or ligature on the catheter

Take the following actions, as necessary:

1. Interrogate the pump. Verify the pump settings and function, see Chapter 9 .
2. Use fluoroscopy or x-rays (radiographs) to evaluate the catheter path.
3. Based on clinical trial experience, a method to determine if the implanted system is delivering drug is to increase the dose slightly. If the patient does not develop Remodulin side effects then an occlusion would be suspected.
4. To confirm an occlusion, conduct a Patency test using the Catheter Patency Kit (Model 8540PAH).

   Note: Medtronic recommends that a technical representative or subject matter expert be consulted or present while the patency procedure is performed.

5. Replace the suspected component.

A.2 Programmer troubleshooting reference guide

Table 13. Quick reference troubleshooting guide

Problem	Possible solution
• The power is ON, but there is no display. • The programmer cannot be operated. • Touchscreen does not respond.	• Turn the programmer OFF, then ON again. • Install new LR6 (AA) batteries in the programmer. • Ensure the batteries are properly installed. • Calibrate touchscreen.
• Telemetry is interrupted or not initiated.	• Ensure that the application card is correctly inserted. • Check the battery status. • Refer to the telemetry failure checklist.
• Power to the programmer suddenly stops.	• Install new LR6 (AA) batteries in the programmer.
• The programmer is not communicating with the printer.	• Clean the infrared lens. • Ensure that the programmer and printer are directly facing and within 1 m (about 3 feet) of each other. • Contact the printer manufacturer for printer-specific troubleshooting information.
• Telemetry cannot be established.	• Refer to the telemetry failure checklist.
• The programmer is operating erratically.	• Move away from any equipment that may be generating electromagnetic interference (EMI), such as MRI equipment, lithotriptor, computer monitor, cell phone, or a motorized wheelchair. EMI may cause a disruption in programmer function.
• An error message or icon appears on the display.	• Refer to instructions in the error messages section.

Refer to the appropriate manual for more information on the Medtronic N'Vision 8840 Programmer or the 8870 Application Card.

For clinician programmer maintenance questions, repairs, and returns, contact the appropriate representative listed in Section 2.4.

A.3 Telemetry failure checklist

The most common corrections for telemetry failures are listed below. Refer to Table 14 for explanations of specific error messages.

- Ensure the programming head is undocked and the cable is fully extended.
- Decrease the distance between the programming head and the pump by pressing the programming head firmly over the implanted pump.
- Hold the programming head steady over the pump, then press the Programming key or select Update Pump.
- If telemetry fails while holding the programming head steady, move the programming head around slowly near the implanted pump. Press the Programming key, or select Update Pump.
- When holding the programming head over the implanted pump, do not drape your hand over the back of the programming head. Hold the programming head at the base.
- Ensure that the programmer batteries are not low or depleted.
- Move away from sources of possible electromagnetic interference (EMI), such as a computer monitor, cell phone, or a motorized wheelchair.

A.4 Activated alarms

Warning: 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 those failures occurred after 4 years of use resulting in the device failing to deliver Remodulin without a 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.

The pump sounds an alarm to indicate certain pump events. There are critical and non-critical alarms.

A critical alarm signals imminent termination of therapy. EOS, tube set interval, and critical pump memory error conditions are considered terminal events. The pump has either stopped or should be stopped since the programmed therapy cannot be guaranteed. A critical alarm is a 3 s dual-tone alarm from the pump that sounds when one of the following conditions occurs:

- Empty reservoir – the estimated reservoir volume is 0.0 mL
- End of Service (EOS) – the pump is at EOS

- Motor stall – the pump detects a stalled motor
- Tube set interval – the pump is stopped for longer than 48 hours
- Critical pump memory error – a critical failure is detected in the pump memory

A non-critical alarm requires a clinician's attention but does not signal imminent termination of therapy. A non-critical alarm is a single-tone alarm from the pump that sounds when one of the following conditions occurs:

- Low reservoir – the estimated reservoir volume is below the low reservoir alarm volume (the default setting is 4.0 mL)
- Elective replacement indicator (ERI) – a time-stamped alarm based on implanted pump longevity that indicates 90 days to EOS
- Non-critical pump memory error – some non-critical data in the pump memory are suspect

Notes:

- Audible alarms can be silenced once activated; however, silencing the alarm does not resolve the alarm condition. The alarm condition is recorded in the Event log.
- All activated alarm events are time-stamped and logged in the Event log.
- Critical alarms take precedence over non-critical alarms. A non-critical alarm will not sound if a critical alarm is sounding.
- If a motor stall is detected and recovered in the shelf state, a pending alarm will be set. An audible alarm will sound after the pump is programmed to the implant state during the initial pump update.
- The pump does not include an occlusion alarm notification.

A.5 Device longevity estimate

Device longevity is dependent upon infusion programming. Until the Elective Replacement Indicator (ERI) condition is reached, the estimated months until ERI are displayed on the Alarms screen. After ERI is reached, the date ERI occurred is displayed. See Section Section 3.1.3 for longevity information.

A.6 Error and informational messages

The clinician programmer displays text (see Table 14 and Table 16) and iconic (see Table 15) error and informational messages. This section includes explanations and actions for messages that may be unclear.

Note: Before referring to Table 14, review Section A.3.

Table 14. Error and informational messages

MESSAGE	EXPLANATION	ACTION
A terminal event has occurred in the pump.	An event has occurred in the pump that cannot be corrected by the programmer.	For the appropriate representative to contact, see Section 2.4.
Alarm Test could not be performed. Please start Alarm Test again.	There is an active alarm and the alarm test cannot be performed at the same time.	Resolve any active alarms.
Based on current Reservoir Volume, Low Reservoir Alarm will be triggered in less than two weeks.	The pump is about to be updated, and the refill interval is set to less than two weeks.	Confirm that the refill interval is appropriate.
Alarms data are invalid.	There is an error in the refill or alarm information in pump memory.	Enter the missing or incorrect information. Update the pump.
Calculated flow rate is too low based on drug concentration, dose and dosing weight.	The minimum therapeutic flow rate that can be programmed into the pump is 0.048 mL/day. Flow rates below 0.048 mL/day are not expected. The offending parameter will not be made pending.	Review the pending values for drug concentration, dose and dosing weight and make corrections as necessary. If the values are correct, contact Medtronic Technical Support.
Drug infusion data are invalid.	There is an error in the infusion information in pump memory.	Enter the missing or incorrect information. Update the pump.
ERI occurred.	The pump has reached ERI condition.	Replace pump within 90 days of ERI.
Incompatible Version	The pump and programmer software are not compatible. The pump was programmed with a version of software that is not compatible with the current application card.	For the appropriate representative to contact, see Section 2.4.
Incomplete pump update can put the pump in stopped pump mode.	Canceled or interrupted telemetry can put the pump in the stopped pump mode.	Continue telemetry and make sure the pump update process is completed without any warning message.
Invalid Telemetry Reposition programming head.	Interference occurred during telemetry or telemetry was interrupted. The pump did not respond.	Reposition the programming head within 4 cm (1.5 in) of the pump, or move away from sources of electrical or magnetic interference. Continue telemetry, or select Cancel to return to the previous screen.

Table 14. Error and informational messages (continued)

MESSAGE	EXPLANATION	ACTION
Magnet was detected. Please remove magnet before programming.	A magnet was detected on the programming head and telemetry was canceled.	Remove the magnet, and continue telemetry. Do not place the magnet on the printer or within 10 cm of the implanted pump.
Notes data are invalid.	There is an error in the notes information in pump memory.	Enter the missing or incorrect information. Update the pump.
Patient information data are invalid.	There is an error in the patient information in pump memory.	Enter the missing or incorrect information. Update the pump.
Pump and catheter data are invalid.	There is an error in the pump and catheter information in pump memory.	Enter the missing or incorrect information. Update the pump.
Pump is in Undefined State	The pump status message returned to the programmer is invalid or may have changed.	For the appropriate representative to contact, see Section 2.4.
Pump Memory Error	There is an error in the information in pump memory.	Verify all programmed data are correct and pump status appears normal, then retry telemetry. If the pump memory error persists, go to the Patient Information screen and interrogate the pump. All current programming changes in the programmer will be lost. Reenter the programming date and update the pump.
Pump is in Safe State	A memory error has occurred in the pump and data has been restored from RAM.	Review the Patient, Pump and Catheter, infusion, and Alarm parameters and make corrections as necessary. Update the pump whether or not corrections were made.
Pump Status is Unknown	Telemetry was incomplete or canceled and the exact pump status cannot be determined.	Reposition the programming head and retry telemetry.
Remove all residual volume before refilling. For rate accuracy, refill pump before volume decreases below 1 mL.	Removing any residual solution before refilling the reservoir ensures the concentration and volume of drug in the reservoir is as intended. Filling the reservoir before the volume reaches 1 mL ensures flow rate accuracy.	Before entering a new reservoir volume, make sure any old solution was completely removed from the pump before new solution was added to the reservoir.

Table 14. Error and informational messages (continued)

MESSAGE	EXPLANATION	ACTION
Start a new programming session. All current data will be lost.	Selecting the Interrogate button during a programming session will end the current session without saving the new pump settings.	Select OK to start a new session. Select Cancel to continue the current session.
WARNING: Pump motor will stop. Pump must be restarted within 48 hours to prevent pump damage. Consult PAH physician to ensure alternative means of drug delivery will start immediately after pump is stopped. You are about to stop a Bolus in progress: Bridge Bolus. Do you want to stop pump. Note: the bolus portion of the message was due to prior programming.	Selecting Stopped Pump mode will stop the pump motor and stop drug flow through the pump tubing. If the pump is stopped for more than 48 hours, the tubing may no longer be patent.	Use Stopped Pump mode for periods of 48 hours or less. Use Minimum Rate mode for longer periods.
The calibration constant is corrupted.	The calibration constant is corrupt and the pump cannot be updated.	For the appropriate representative to contact, see Section 2.4.
The device ID is invalid.	The pump ID is invalid and the pump cannot be updated.	For the appropriate representative to contact, see Section 2.4.
The programmer batteries are low. Please turn the programmer off and replace the batteries.	The programmer batteries are low and may not last an entire programming session.	Turn the programmer off. Replace the programmer batteries.
The pump is in Shelf State.	The pump has not been programmed and is in Minimum Rate mode with alarms disabled.	Program the pump at implant.
The pump is in Shelf State. The pump has a pending alarm. Check the pump Event log and call Medtronic. The alarm will sound after pump update.	The pump has a pending alarm.	Check the pump Event log and call Medtronic.
The Session Data Manager is full. Please press the OK button to open the Session Data Manager and delete old records. Press Cancel to proceed without deleting any records. In this case, data will not be saved.	No new files can be saved to the Session Data Manager until space is made available by deleting old files.	Press OK, and delete unneeded records.

Table 14. Error and informational messages (continued)

MESSAGE	EXPLANATION	ACTION
Therapy Stop Inactive Use Minimum Rate mode.	Therapy Stop is only available from the Drug delivery desktop screen.	To change the pump to Minimum Rate mode without going to the Drug delivery desktop screen, select Minimum Rate mode and update the pump.
Wrong Pump Telemetry cancelled	The most recent pump interrogated is not the same pump being updated and telemetry has been canceled.	Do one of the following: 1. Place the programming head over the pump that was initially interrogated and update the pump to the new settings. 2. Reinterrogate the current pump. All current programming changes will be lost and must be re-entered before updating the pump.
Wrong Pump Telemetry cancelled	The application selected does not match the pump type.	Exit the application and start the correct application.

Table 15. Iconic error messages

Error message	Explanation
	Application card missing Reinsert card to start a new session.
	Application card error For the appropriate representative to contact, see Section 2.4.
	Therapy-stop key pressed with no application active
	Programming key pressed with no application active
	Hardware/software failure message For the appropriate representative to contact, see Section 2.4.

A.7 Event log

Note: At every patient visit the clinician must review the Event log for any pump failures that have occurred since the last visit.

Events are pump conditions that are recorded and displayed in the Event log in chronological order. The following content is also recorded:

- an event description or number (events with only an event number are for diagnostic purposes)
- the date and time the event occurred

Table 16 lists potential Event log messages along with actions for resolution, if required.

Note: Alarms may be silenced if appropriate.

Table 16. Event log messages and explanations

Code	Message	Action
0	End of Service (EOS) Occurred	Replace the pump.
1	Reset Occurred	Contact Medtronic.
3	Motor Stall Occurred	A pump replacement may be needed. Contact Medtronic.
4	Stopped Pump May Exceed Tube Set	If desired, restart pump and verify flow rate.
5	Critical Memory Error Occurred	Contact Medtronic.
6	Empty Reservoir Alarm Occurred	Refill pump and update refill-related parameters.
7	Pump in Safe State	Contact Medtronic.
8	Infusion Handshake Error	None required.
13	Pump Stopped Due to Safety Count	Contact Medtronic.
14	Pump Stopped Due to Stop Command	None required.
15	Pump Stopped Due to Off State	None required.
16	Pump Restarted Due to Restart Command	None required.
18	Event Status Cleared	None required.
19	An Active Audible Alarm Was Silenced	None required.
21	Pump Refill Occurred[a]	None required.
22	Clock Set[a]	None required.
23	Infusion (Prescription) Changes Occurred[a]	None required.
24	Patient Configuration Change Occurred[a]	None required.
26	Infusion Bolus Command Received	None required.
30	Stack Overflow	Contact Medtronic.

Table 16. Event log messages and explanations (continued)

Code	Message	Action
1A	Motor Stall Recovery Occurred	A pump replacement may be needed. Contact Medtronic.
2B	Reset Occurred—Low Battery	Contact Medtronic.
2C	Reset Occurred—Watchdog	Contact Medtronic.
2D	Reset Occurred—Telemetry Command	Contact Medtronic.
2E	Time in RAM Corrupt	None required.
2F	Stack Pointer Error	Contact Medtronic.
0A	Low Reservoir Alarm Occurred	Refill pump and update refill-related parameters.
0D	Elective Replacement Indicator (ERI) Occurred	Replace pump within 90 days of ERI.
0E	Noncritical Memory error occurred	Contact Medtronic. Verify that all programmed data are correct and pump status appears normal.
0F	Hybrid Trim Parameters Error	Contact Medtronic.

[a] Occurs at every pump refill or programming session.

A.8 Reservoir valve activation

Activation of the pump reservoir valve seals the pump reservoir valve closed. Unusual resistance or the inability to inject the entire fill volume may indicate activation of the pump reservoir valve. If the valve closes, the reservoir contents must be delivered or removed before completing the filling of the pump. Procedural delays can occur.

If you have activated the reservoir valve, complete steps 1 through 7 that follow.

1. Discontinue injection.
2. Close the clamp.
3. Remove the syringe with prescribed fluid and attached filter.
4. Attach an empty 20 mL syringe to the extension set.
5. Open the clamp and aspirate until all fluid and air are removed.
6. Close the clamp and remove the syringe containing the aspirate from the extension set and discard the syringe.
7. For a new system implant scenario, continue with the steps in Section 10.4.5. For a pump replacement scenario, continue with the steps in Section 14.3.5.

B Pump refill and longevity estimation tables

B.1 Pump refill and longevity estimation tables

The pump needs to be replaced when one of the following events occurs:

- 7 years have elapsed since the pump was implanted
- The pump motor has completed 40,000 motor revolutions

Pump longevity is a function of flow rate. Longevity decreases when the flow rate is greater than 0.94 mL/day. The following equation (see Figure 113) can be used to estimate longevity based on the therapeutic flow rate (see Figure 115) and an average delivery rate of 0.06 mL per motor revolution:

Figure 113. Equation to estimate longevity

$$longevity = smaller\ of \left(\frac{40000 * 0.06}{Q_{ther} * 365} \right) or\ 7\ years$$

Table 17 defines the parameters presented in the equation.

Table 17. Parameters for longevity equation

Parameter	Definition	Units
longevity	longevity period (time before pump needs to be replaced)	years
Q_{ther}	therapeutic flow rate	mL/day
40000	number of motor revolutions during the life of the device	
0.06	average delivery rate (in mL) per motor revolution	
365	days per year	

Refill interval is a function of flow rate and pump reservoir volume, as shown in the following equation (see Figure 114):

Figure 114. Equation to establish refill interval

$$refill = smaller\ of \left(\frac{V_{reservoir} - V_{alarm}}{Q_{ther}} \right) or\ 112\ days$$

Table 18 defines the parameters presented in the equation.

Table 18. Parameters for refill interval equation

Parameter	Definition	Units
refill	refill interval (time before low reservoir alarm volume is reached)	days
$V_{reservoir}$	volume of drug in the reservoir	mL
V_{alarm}	low reservoir alarm threshold volume	mL
Q_{ther}	therapeutic flow rate	mL/day

The therapeutic flow rate is a function of the patient's dose, dosing weight, and drug concentration, as shown in the following equation:

Figure 115. Equation to determine therapeutic flow rate

$$Q_{ther} = \frac{d * W_{dosing} * 1440}{C_{drug} * 10^6}$$

Table 19 defines the parameters presented in the equation:

Table 19. Parameters for therapeutic flow rate equation

Parameter	Definition	Units
Q_{ther}	therapeutic flow rate	mL/day
d	patient's dose	ng/kg/min
W_{dosing}	patient's dosing weight	kg
C_{drug}	drug concentration	mg/mL
1440	minutes per day	
10^6	number of nanograms in a milligram	

The following table shows estimates of longevity and refill intervals for various combinations of dose, dosing weight, 10 mg/mL drug concentration, and 40 mL pump reservoir volume.

Table 20. Pump refill and longevity estimation for 40 mL pump with 4 mL Low Reservoir Alarm and 10 mg/mL Remodulin® (treprostinil) Injection concentration

		Dose (ng/kg/min)										
Dosing Weight (kg)		**40**	**50**	**60**	**70**	**80**	**90**	**100**	**110**	**120**	**130**	**140**
50	Refill (weeks)	16.0	14.3	11.9	10.2	8.9	7.9	7.1	6.5	6.0	5.5	5.1
	Longevity (years)	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	6.5
55	Refill (weeks)	16.0	13.0	10.8	9.3	8.1	7.2	6.5	5.9	5.4	5.0	4.6
	Longevity (years)	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	6.9	6.4	5.9
60	Refill (weeks)	14.9	11.9	9.9	8.5	7.4	6.6	6.0	5.4	5.0	4.6	4.3
	Longevity (years)	7.0	7.0	7.0	7.0	7.0	7.0	7.0	6.9	6.3	5.9	5.4
65	Refill (weeks)	13.7	11.0	9.2	7.8	6.9	6.1	5.5	5.0	4.6	4.2	3.9
	Longevity (years)	7.0	7.0	7.0	7.0	7.0	7.0	7.0	6.4	5.9	5.4	5.0
70	Refill (weeks)	12.8	10.2	8.5	7.3	6.4	5.7	5.1	4.6	4.3	3.9	3.6
	Longevity (years)	7.0	7.0	7.0	7.0	7.0	7.0	6.5	5.9	5.4	5.0	4.7
75	Refill (weeks)	11.9	9.5	7.9	6.8	6.0	5.3	4.8	4.3	4.0	3.7	3.4
	Longevity (years)	7.0	7.0	7.0	7.0	7.0	6.8	6.1	5.5	5.1	4.7	4.3
80	Refill (weeks)	11.2	8.9	7.4	6.4	5.6	5.0	4.5	4.1	3.7	3.4	3.2
	Longevity (years)	7.0	7.0	7.0	7.0	7.0	6.3	5.7	5.2	4.8	4.4	4.1
85	Refill (weeks)	10.5	8.4	7.0	6.0	5.3	4.7	4.2	3.8	3.5	3.2	3.0
	Longevity (years)	7.0	7.0	7.0	7.0	6.7	6.0	5.4	4.9	4.5	4.1	3.8
90	Refill (weeks)	9.9	7.9	6.6	5.7	5.0	4.4	4.0	3.6	3.3	3.1	2.8
	Longevity (years)	7.0	7.0	7.0	7.0	6.3	5.6	5.1	4.6	4.2	3.9	3.6

Table 20. Pump refill and longevity estimation for 40 mL pump with 4 mL Low Reservoir Alarm and 10 mg/mL Remodulin® (treprostinil) Injection concentration (continued)

		Dose (ng/kg/min)										
Dosing Weight (kg)		**40**	**50**	**60**	**70**	**80**	**90**	**100**	**110**	**120**	**130**	**140**
95	Refill (weeks)	9.4	7.5	6.3	5.4	4.7	4.2	3.8	3.4	3.1	2.9	2.7
	Longevity (years)	7.0	7.0	7.0	6.9	6.0	5.3	4.8	4.4	4.0	3.7	3.4
100	Refill (weeks)	8.9	7.1	6.0	5.1	4.5	4.0	3.6	3.2	3.0	2.7	2.6
	Longevity (years)	7.0	7.0	7.0	6.5	5.7	5.1	4.6	4.1	3.8	3.5	3.3
105	Refill (weeks)	8.5	6.8	5.7	4.9	4.3	3.8	3.4	3.1	2.8	2.6	2.4
	Longevity (years)	7.0	7.0	7.0	6.2	5.4	4.8	4.3	4.0	3.6	3.3	3.1
110	Refill (weeks)	8.1	6.5	5.4	4.6	4.1	3.6	3.2	3.0	2.7	2.5	2.3
	Longevity (years)	7.0	7.0	6.9	5.9	5.2	4.6	4.1	3.8	3.5	3.2	3.0
115	Refill (weeks)	7.8	6.2	5.2	4.4	3.9	3.5	3.1	2.8	2.6	2.4	2.2
	Longevity (years)	7.0	7.0	6.6	5.7	5.0	4.4	4.0	3.6	3.3	3.1	2.8
120	Refill (weeks)	7.4	6.0	5.0	4.3	3.7	3.3	3.0	2.7	2.5	2.3	2.1
	Longevity (years)	7.0	7.0	6.3	5.4	4.8	4.2	3.8	3.5	3.2	2.9	2.7
125	Refill (weeks)	7.1	5.7	4.8	4.1	3.6	3.2	2.9	2.6	2.4	2.2	2.0
	Longevity (years)	7.0	7.0	6.1	5.2	4.6	4.1	3.7	3.3	3.0	2.8	2.6
130	Refill (weeks)	6.6	5.3	4.4	3.8	3.3	2.9	2.6	2.4	2.2	2.0	1.9
	Longevity (years)	7.0	6.8	5.6	4.8	4.2	3.8	3.4	3.1	2.8	2.6	2.4
135	Refill (weeks)	6.2	4.9	4.1	3.5	3.1	2.7	2.5	2.2	2.1	1.9	1.8
	Longevity (years)	7.0	6.3	5.2	4.5	3.9	3.5	3.1	2.9	2.6	2.4	2.2

Table 20. Pump refill and longevity estimation for 40 mL pump with 4 mL Low Reservoir Alarm and 10 mg/mL Remodulin® (treprostinil) Injection concentration (continued)

		Dose (ng/kg/min)										
Dosing Weight (kg)		**40**	**50**	**60**	**70**	**80**	**90**	**100**	**110**	**120**	**130**	**140**
140	Refill (weeks)	5.8	4.6	3.8	3.3	2.9	2.6	2.3	2.1	1.9	1.8	1.6
	Longevity (years)	7.0	5.9	4.9	4.2	3.7	3.3	2.9	2.7	2.5	2.3	2.1
145	Refill (weeks)	5.4	4.3	3.6	3.1	2.7	2.4	2.2	2.0	1.8	1.7	1.5
	Longevity (years)	6.9	5.5	4.6	4.0	3.5	3.1	2.8	2.5	2.3	2.1	2.0
150	Refill (weeks)	5.1	4.1	3.4	2.9	2.6	2.3	2.0	1.9	1.7	1.6	1.5
	Longevity (years)	6.5	5.2	4.3	3.7	3.3	2.9	2.6	2.4	2.2	2.0	1.9

C Average time to 50% drug concentration (new system implant)

C.1 Average time to 50% drug concentration (new system implant)

The values in the following table represent the average expected times from external line shutoff (assuming the 20% patient dose) to 50% drug concentration delivered by the Implantable System for Remodulin. After the external line is turned off following a new system implant, the drug concentration continues to increase as more drug is delivered from the implanted pump. The time it takes to reach 50% of the prescribed dose from the time the external line is turned off is dependent on the therapeutic flow rate.

The following equation can be used to estimate the time to reach 50% of the prescribed dose after external line shutoff.

Figure 116. Equation to estimate the time to reach 50% of the prescribed dose (see the table immediately after the figure for more information)

$$t_{turnoff\text{-}50\%} = \frac{\Delta V_{turnoff\text{-}50\%}}{Q_{ther}} * 24$$

ΔV	Average delivered volume from external line turnoff to 50% • 10% turnoff = 0.054 • 20% turnoff = 0.038 • 30% turnoff = 0.028	mL

Table 21 defines the parameters presented in the equation.

Table 21. Parameters for time to 50% equation

Parameter	Definition	Units
$t_{turnoff\text{-}50\%}$	time to reach 50% of prescribed dose after external line turn-off	hours
$\Delta V_{turnoff\text{-}50\%}$	Average delivered volume from external line turn-off to 50%	mL
Q_{ther}	therapeutic flow rate	mL/day
24	hours per day	

The equation for calculating therapeutic flow rate is defined in Appendix B.

The following table shows estimates of the time between the default 20% patient dose-turn off of the external line and the 50% dose for various combinations of dose, dosing weight, and drug concentration.

Table 22. 10 mg/mL Remodulin® (treprostinil) Injection concentration—Average time (hours) to 50% drug concentration after turning off the external line following a new system implant (default 20% patient dose turn-off)

	Dose (ng/kg/min)												
Dosing Weight (kg)	**20**	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**	**110**	**120**	**130**	**140**
50	6.3	4.2	3.2	2.5	2.1	1.8	1.6	1.4	1.3	1.2	1.1	1.0	0.9
55	5.8	3.8	2.9	2.3	1.9	1.6	1.4	1.3	1.2	1.0	1.0	0.9	0.8
60	5.3	3.5	2.6	2.1	1.8	1.5	1.3	1.2	1.1	1.0	0.9	0.8	0.8
65	4.9	3.2	2.4	1.9	1.6	1.4	1.2	1.1	1.0	0.9	0.8	0.7	0.7
70	4.5	3.0	2.3	1.8	1.5	1.3	1.1	1.0	0.9	0.8	0.8	0.7	0.6
75	4.2	2.8	2.1	1.7	1.4	1.2	1.1	0.9	0.8	0.8	0.7	0.6	0.6
80	4.0	2.6	2.0	1.6	1.3	1.1	1.0	0.9	0.8	0.7	0.7	0.6	0.6
85	3.7	2.5	1.9	1.5	1.2	1.1	0.9	0.8	0.7	0.7	0.6	0.6	0.5
90	3.5	2.3	1.8	1.4	1.2	1.0	0.9	0.8	0.7	0.6	0.6	0.5	0.5
95	3.3	2.2	1.7	1.3	1.1	1.0	0.8	0.7	0.7	0.6	0.6	0.5	0.5
100	3.2	2.1	1.6	1.3	1.1	0.9	0.8	0.7	0.6	0.6	0.5	0.5	0.5
105	3.0	2.0	1.5	1.2	1.0	0.9	0.8	0.7	0.6	0.5	0.5	0.5	0.4
110	2.9	1.9	1.4	1.2	1.0	0.8	0.7	0.6	0.6	0.5	0.5	0.4	0.4
115	2.8	1.8	1.4	1.1	0.9	0.8	0.7	0.6	0.6	0.5	0.5	0.4	0.4
120	2.6	1.8	1.3	1.1	0.9	0.8	0.7	0.6	0.5	0.5	0.4	0.4	0.4
125	2.5	1.7	1.3	1.0	0.8	0.7	0.6	0.6	0.5	0.5	0.4	0.4	0.4
135	2.3	1.6	1.2	0.9	0.8	0.7	0.6	0.5	0.5	0.4	0.4	0.4	0.3
145	2.2	1.5	1.1	0.9	0.7	0.6	0.5	0.5	0.4	0.4	0.4	0.3	0.3
155	2.0	1.4	1.0	0.8	0.7	0.6	0.5	0.5	0.4	0.4	0.3	0.3	0.3
165	1.9	1.3	1.0	0.8	0.6	0.5	0.5	0.4	0.4	0.3	0.3	0.3	0.3
175	1.8	1.2	0.9	0.7	0.6	0.5	0.5	0.4	0.4	0.3	0.3	0.3	0.3

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Medtronic

Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432
USA
www.medtronic.com
+1 763 514 4000

Medtronic USA, Inc.
Toll-free in the USA (24-hour technical consultation for physicians and medical professionals)
Bradycardia: +1 800 505 4636
Tachycardia: +1 800 723 4636

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DelIVery for Pulmonary Arterial Hypertension (PAH) Clinical Study

Clinical Study Summary

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Contents

1 Summary of clinical results

1.1 Introduction

The DellVery for Pulmonary Arterial Hypertension (PAH) Clinical Study demonstrated the Model 10642 Implantable Intravascular Catheter is safe when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin™[1].

1.2 Study purpose

The purpose of the clinical trial was to evaluate the safety profile of the Model 10642 Implantable Intravascular Catheter, a component of the PAH Implantable Vasodilator Therapy (PIVoT) system. The PIVoT system includes the SynchroMed II Implantable Infusion System (Model 8637), the Implantable Intravascular Catheter (with sutureless connector) (investigational, Model 10642), and the N'Vision Clinician Programmer (Model 8840) with application software card (Model 8870). This system will be used to deliver Remodulin (treprostinil) Injection, a currently marketed pharmaceutical. This report provides safety information on the Model 10642 Implantable Intravascular Catheter, which is applicable to and supports market release of the Model 8201 Implantable Intravascular Catheter and Implantable System for Remodulin.

1.3 Study scope, design, and methods

The clinical study was designed as a multi-center, prospective, single arm, non-randomized open label Investigational Device Exemption (IDE) clinical study. Up to 70 subjects at 10 centers were planned for implant and follow-up. This study was conducted in the United States. The study enrolled subjects who met the approved Remodulin indication, using the approved concentrations, and approved intravenous route of administration and who met all inclusion and no exclusion criteria.

Implanted subjects were seen at scheduled follow-up visits; 1 week, 6 weeks, 3 months, 6 months, 12 months, and then every 6 months thereafter. The primary endpoint was evaluated when all active subjects completed the 6 month follow-up visit, and a minimum of 22,000 patient days among implanted subjects were accumulated.

1.4 Subject inclusion and exclusion criteria

Patients who met all inclusion and no exclusion criteria were eligible.

Inclusion criteria

- Patient is 18 years of age or older
- Patient (or patient's legally authorized representative) is willing and able to provide written informed consent
- Patient is willing and able to comply with the protocol, including required follow-up visits
- Patient is diagnosed with Pulmonary Arterial Hypertension (World Health Organization (WHO) Category Group 1 [by the WHO Clinical classification system]), including:
  - Idiopathic (IPAH)
  - Heritable PAH (HPAH)
  - Associated with PAH (APAH), with exceptions as noted in exclusion criteria below
- Patient is receiving continuous infusion of Remodulin therapy via intravenous delivery using an external drug delivery pump system. Patient has been at a stable Remodulin dose (no change in dose) for at least 4 weeks.
- Patient's anticoagulation therapy can be managed to permit safe device implantation
- Patient has no history of pulmonary embolism since the initiation of subcutaneous or IV therapy for PAH

Exclusion criteria

- Patient is a woman who is pregnant, nursing, or of child bearing potential and is not on a reliable form of birth control
- Patient is enrolled, has participated within the last 30 days, or is planning to participate in a concurrent drug and/or device study during the course of this clinical trial. Co-enrollment in concurrent trials is only allowed with documented pre-approval from the Medtronic study manager that there is not a concern that co-enrollment could confound the results of this trial
- Patient has been initiated on a new oral PAH therapy in the last 2 months
- Patient has had a recent (within 3 months) or otherwise unresolved infection requiring antibiotic treatment
- Patient is diagnosed with PAH associated with hemoglobinopathies (sickle cell anemia, thalassemia), HIV, schistosomiasis, portal hypertension, pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis
- Patient is implanted with electrical stimulation medical devices(s) anywhere in the body (e.g., cardiac pacemakers, implantable cardioverter defibrillators (ICDs), spinal cord stimulators). This includes implanted leads and electrodes or abandoned leads and electrodes from an explanted device
- Patient is diagnosed with chronic kidney disease (serum creatinine > 2.5 mg/dl) within 90 days prior to baseline visit; chronic kidney disease is defined as that lasting or expected to last more than 3 months
- Patient is a person for whom the implantable vascular catheter length of 80 cm was excessively long or too short to be properly implanted
- Patient has an existing external catheter(s) that would remain in place after the pump implant
- Patient is a person for whom the implantable pump cannot be implanted 2.5 cm or less from the skin surface
- Patient is a person whose body size is not sufficient to accept implantable pump bulk and weight
- Patient is at increased susceptibility to systemic or soft tissue infections as determined by physician
- Patient is Functional Class IV (New York Heart Association (NYHA))

[1] Remodulin is a product of United Therapeutics Corporation.

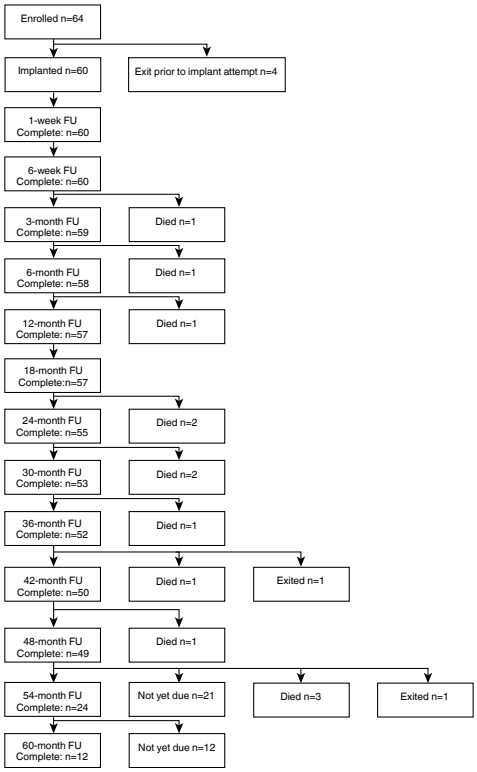
1.5 Results

The first subject was enrolled on June 14, 2011, and the final subject was enrolled on November 20, 2012. A total of 64 subjects were enrolled in the DellVery for PAH clinical study at 10 investigational sites in the United States. Of the 64 subjects, there were 60 attempted implants and all 60 were successfully implanted with the system.

It was pre-specified in the study protocol that the primary objective of the study would be analyzed when 22,000 patient days of follow-up had occurred and all active subjects completed the 6 month follow-up visit. The primary endpoint data in this report were reported per protocol and includes any visit or event that occurred on or before June 21, 2013. All other data in this report is from data collected on case report forms on or before January 11, 2017 and received at Medtronic on or before March 3, 2017 unless otherwise specified/noted.

Of the 60 implanted subjects, there were 89,935 days of follow-up (range 87-1996 days per subject). Study subject disposition is displayed in Figure 1

Figure 1. Enrolled subject status enrollment flow chart



Subject demographics

Table 1 presents baseline information for all 64 subjects enrolled, including the 4 subjects who exited prior to implant, and the 60 subjects who were implanted.

Table 1. Baseline demographics

Subject characteristics	Non-implanted subjects (n = 4)	Implanted subjects (n = 60)	Total subjects (n = 64)
Gender (N, %)			
Male	1 (25%)	12 (20%)	48 (80%)
Female	3 (75%)	48 (80%)	51 (80%)
Age (years)			
Mean ± Standard deviation	49.8 ± 16.9	50.1 ± 13.5	50.1 ± 13.5
Median	52.5	52.0	52.0
25th Percentile - 75th Percentile	36 - 64	38 - 61	38 - 61
Minimum – Maximum	29 - 65	24 - 74	24 - 74
Race / Ethnic Origin (N, %)			
Subject/physician chose not to provide information	0 (0%)	0 (0%)	0 (0%)
Not reportable per local laws or regulations	0 (0%)	0 (0%)	0 (0%)
American Indian or Alaska Native	0 (0%)	0 (0%)	0 (0%)
Asian	0 (0%)	2 (3%)	2 (3%)

Table 1. Baseline demographics (continued)

Subject characteristics	Non-implanted subjects (n = 4)	Implanted subjects (n = 60)	Total subjects (n = 64)
Black or African American	0 (0%)	3 (5%)	3 (5%)
Hispanic or Latino	1 (25%)	8 (13%)	9 (14%)
Native Hawaiian or Pacific Islander	0 (0%)	0 (0%)	0 (0%)
White or Caucasian	3 (75%)	47 (78%)	50 (78%)
Two or more races	0 (0%)	0 (0%)	0 (0%)
Other race	0 (0%)	0 (0%)	0 (0%)

Primary objectives

There was 1 primary endpoint. The objective was to demonstrate that the Model 10642 Implantable Intravascular Catheter is safe when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin.

The results of the primary safety analysis, summarized in Table 2, demonstrate that the primary safety objective was met, demonstrating that the Model 10642, when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin, is safe. This was shown by the low rate of catheter-related complications compared to an objective performance criteria derived from literature.

Published data in the PAH population suggests a rate of central venous catheter (CVC) systemic infections for bloodstream infections (BSI) at 0.43[2] to 1.13[3] per 1000 patient days and site infections at 0.26[4] to 0.87[5] per 1000 patient days while complications from catheter thrombosis, mechanical dysfunction, and catheter dislocation in the general CVC population contribute another 0.36[6, 7] -0.51[8] events per 1000 patient days. This leads to a combined rate of catheter-related complications of up to 2.5 per 1000 patient days.

Table 2. Summary of primary objective results

Data cut-off	Performance goal	Patient days	Catheter-related complications	Catheter-related complications per 1000 days	One-sided upper 97.5% confidence bound	P-value
June 21, 2013	Rate per 100 days < 2.5	22,013	6	0.27	0.59	<0.0001
January 11, 2017		89,935	7	0.08	0.16	<0.0001

Ancillary objectives

The study further characterized the system effectiveness and symptom relief, quality of life, and ease of use, healthcare utilization assessments, and subject/caregiver involvement in system management of the system through the ancillary objectives. These objectives are descriptive in nature and there were no powered hypotheses to be tested. Table 3 presents a summary of the ancillary objectives.

As expected, efficacy variables including Quality of Life (QoL) (CAMPHOR and EQ-5D questionnaires), 6-Minute Walk, New York Heart Association Functional Classification showed little or no change when comparing the external pump (baseline) to the implanted pump; this was expected since the treatment therapy (Remodulin) is the same with the external and internal pumps. In addition, similar results were observed within a third QoL assessment, the FACIT-TS-G questionnaire. One hundred percent of subjects rated their overall satisfaction with the implantable system as good, very good or excellent at both 6 and 26 weeks.

Table 3. Summary of ancillary objectives results

Objective	Results
To characterize percent change of 6-minute walk test distance from baseline to 6 weeks post-implant	Mean percent increase in 6-minute walk from baseline to 6 weeks post-implant: 0.2% ± 19.3% 95% confidence interval: -4.9 - 5.2%
To characterize changes in quality of life	CAMPHOR (QoL Scale) change from baseline to 6 months. EQ-5D Mean absolute change at 6 months ± S.D.: -0.01 ± 0.10 95% confidence interval: -0.04 – 0.02
To characterize the incidence of adverse events	Subject experience included 64 enrolled subjects, and 246 years of implanted follow-up time in 60 subjects. During that time, there were 1222 Adverse Events: 325 adverse events related to procedure, drug pump, catheter, programmer, Remodulin Injection, refill process, catheter patency test, implant tools, or Model 8540 Catheter Access Port Kit 897 adverse events not related to the items listed above.
To characterize healthcare utilization (hospitalizations, emergency room visits, and urgent clinic visits)	At 12 months post-implant: 45.6% had been hospitalized. 53.3% had been in the ER or hospitalized.

[2] Dickinson MG, Schölvinck EH, Boonstra A, Vonk-Noordegraaf A, Snijder RJ, Berger RM. Low complication rates with totally implantable access port use in epoprostenol treatment of pulmonary hypertension. J Heart Lung Transplant. 2009 Mar; 28(3): 273-9.

[3] Kallen AJ, Lederman E, Balaji A, et al. Bloodstream infections in patients given treatment with intravenous prostanoids. Infect Control Hosp Epidemiol. 2008 Apr; 29(4): 342-9.

[4] Oudiz RJ, Widlitz A, Beckmann XJ, et al. Micrococcus-associated central venous catheter infection in patients with pulmonary arterial hypertension. Chest. 2004 Jul; 126(1): 90-4.

[5] Akagi S, Matsubara H, Ogawa A, et al. Prevention of catheter-related infections using a closed hub system in patients with pulmonary arterial hypertension. Circ J. 2007;71:559-564.

[6] Smith JR, Friedell ML, Cheatham ML, Martin SP, Cohen MJ, Horowitz JD. Peripherally inserted central catheters revisited. Am J Surg. 1998;176:208-211.

[7] Bozzetti F, Mariani L, Boggio Bertinet D, et al. Central venous catheter complications in 447 patients in home parenteral nutrition: an analysis of over 100,000 catheter days. Clin Nutr. 2002;21(6):45-485.

[8] Moureau N, Poole S, Murdock MA, Gray SM, Semba CP. Central venous catheters in home infusion care: outcomes analysis in 50,470 patients. J Vasc Interv Radiol. 2002;13:1009-1016.

1.6 Adverse events summary

All AEs were reported throughout the study, starting at subject enrollment. Documented pre-existing conditions were not considered AEs unless the nature or severity of the condition had worsened.

Adverse Events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) which uses a 5-step hierarchical system, starting with the Lowest Level Term (LLT) (level 1) or diagnosis and progressively losing specificity up to a System Organ Class (SOC) (level 5). Preferred Terms (PT) are used in the summary tables except catheter dislodgement, which is an LLT.

Anticipated adverse events were collected in the study. Table 4 lists the events and the time frame for which they were considered anticipated. An event was considered anticipated if the onset and resolution occurred within the specified timeframe.

Table 4. Anticipated AEs related to implant procedure

Event description	Time frame (hours) from the surgical procedure
Anesthesia-related nausea/vomiting	24
Low-grade fever (<100°F or <37.8°C)	48
Pocket site / incisional pain	72
Mild to moderate bruising / ecchymosis	168
Sleep problems (insomnia)	72
Back pain related to lying on the table	72
Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure	72
Mild exacerbation of PAH symptoms	24

All AEs and deaths were reviewed by an independent Adverse Events Adjudication Committee (AEAC). The AEAC adjudicated each event for event MedDRA code, seriousness, relatedness and when applicable, complication/observation. The definition of a complication is used for determination of the events counted towards the primary objective analysis. A complication is defined as an adverse event that results in death, involves termination of significant device function, or requires an invasive intervention.

Table 5. Adverse event definitions

General	
Adverse Event (AE)	Any unfavorable medical occurrence in a subject. **Note:** This definition does not imply that there is a relationship between the adverse event and the device under investigation. (ISO14155-1:2003(E) 3.2).
Seriousness	
Serious Adverse Event (SAE)	Serious adverse events include adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, and are life-threatening, a persistent or significant disability/incapacity or a congenital anomaly/birth defect. Other important medical events, based upon appropriate medical judgment, may also be considered Serious Adverse Events if a trial participants' health is at risk and intervention is required to prevent an outcome mentioned. (FDAAA, U.S. Public Law 110-85, Title VIII Section 801).

Results

There were 1222 adverse events reported for 62 out of the 64 enrolled subjects. Of these 1219 involved the 60 subjects who were implanted with the PIVoT system. Three AEs occurred in 2 of the 4 subjects who never attempted implant. Of the 1222 adverse events, 1214 (99.3%) have been fully adjudicated by the AEAC. The timing of the event onset (i.e. pre, during and post-implant) was assessed by the site principal investigator and was not adjudicated by the AEAC. Table 6 is a high-level summary of all adverse events collected in the study.

Table 6. Adverse event summary

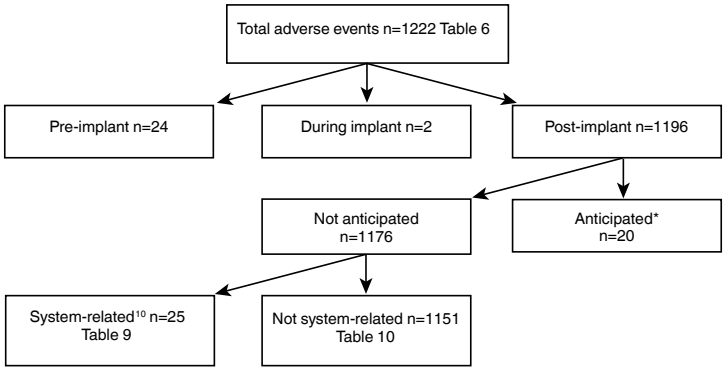
AE timing	Related[a]	Not related	Total adverse events
Pre-implant	1	22	24
During implant[b]	2	0	2
Post-implant	322	874	1196
Total	325	897	1222

[a] Related to procedure, drug pump, catheter, programmer, Remodulin Injection, refill process, catheter patency test, implant tools, or Model 8540 Catheter Access Port Kit.

[b] After skin incision and before completion of skin closure.

There are a number of summary tables in this section. Figure 2 shows how the AE data are categorized in Table 6, Table 7, Table 8, Table 9, and Table 10.

Figure 2. Summary of all adverse events. (System-related means related to the catheter, pump, or programmer.)



1 [10]System-related means related to the catheter, pump, or programmer.
2 *Anticipated events are listed in Table 4.

There were 24 pre-implant AE's in the study. One (infusion site pain) was related to the system/procedure and adjudicated as Implant Procedure and Remodulin related, as this was due to the temporary external peripheral Remodulin infusion line placed at least 1 day prior to implant (part of the implant procedure). Three of the pre-implant AE's were device-related infection from the subject's pre-existing PICC line, 2 AE's were reported for hypokalemia, 2 for vessel site puncture pain, and all other AE's were single events.

Two adverse events with onset assessed by the site as occurring during implant are summarized in Table 7.

Table 7. Adverse events occurring during implant

Preferred term	Description (verbatim from CRF)	Actions taken	Relatedness
Atrial fibrillation	Patient has history of atrial flutter. Per anesthesia note "beginning of procedure, NSR, began intermit atrial fib/flut during access to vein. Continuous Afib with catheter placement." "I spoke directly to Dr. (name redacted) this afternoon and he stated the patient was in normal sinus rhythm at the beginning of the case with "intermittent atrial arrhythmias".	Other diagnostic tests / procedures (noted during cardiac monitoring during the implant procedure.), Medications administered, other actions taken (cardioversion; resolved the atrial fibrillation)	Implant procedure
Pneumothorax	Subject transferred to PACU from OR. Subject was noted to be dyspneic, oxygen saturations 80's and hypotensive, SBP 80's and severe pain. CXR obtained and modest right pneumothorax was seen. The AE is related to placement of implantable catheter. Subject treated with supplemental oxygen (100% non-rebreather mask), fluid bolus administered and Dilaudid IV given for pain. Subject hemodynamically stable and transferred to patient care unit.	Chest X-ray, other diagnostic tests / procedures (1/10/12 chest x-ray post-op - moderate right pneumothorax), prolongation of existing hospitalization, medications administered, other actions taken (100% non-rebreather oxygen mask)	Implant procedure, implant tool(s)

Following the 60 implants and excluding anticipated adverse events, there were 1176 post-implant adverse events, which are summarized in Table 8.

Table 8. Post-implant adverse event summary excluding anticipated

Adverse event classification	Number of events (number of subjects, % of subjects) (n=60)
Serious	
Yes	190 (46, 76.67%)
No	985 (60, 100.00%)
Unknown	1 (1, 1.67%)
Unanticipated[a]	0 (0, 0.0%)
Procedure relatedness	
Related	149 (54, 90.00%)
Implant procedure	137 (54, 90.00%)
System modification	12 (5, 8.33%)
Not related	1027 (60, 100.00%)
Unknown	0 (0, 0.0%)
System relatedness	
Related	25 (19, 31.67%)
Model 10642 catheter	6 (3, 5.00%)
SynchroMed II pump	19 (16, 26.67%)
Not related	1151 (60, 100.00%)

Table 8. Post-implant adverse event summary excluding anticipated (continued)

Adverse event classification	Number of events (number of subjects, % of subjects) (n=60)
Unknown	0 (0, 0.0%)
Remodulin injection	
Related	139 (40, 66.67%)
Not related	1031 (60, 100.00%)
Unknown[b]	6 (4, 6.67%)
Refill process	
Related	95 (38, 63.33%)
Not related	1080 (60, 100.00%)
Unknown	1 (1, 1.67%)
Implant tool	
Related	1 (1, 1.67%)
Not related	1175 (60, 100.00%)
Unknown	0 (0, 0.0%)
Model 8540 catheter access port kit	
Related	0 (0, 0.0%)
Not related	1176 (60, 100.00%)
Unknown	0 (0, 0.0%)
Catheter patency test	
Related	0 (0, 0.0%)
Not related	1176 (60, 100.00%)
Unknown	0 (0, 0.0%)
Total	**1176 (60, 100.00%)**

[a] Four pump events occurred at the time of this report, (1 high resistant battery ERI, 3 pump motor stalls). The individual events are not considered unanticipated. Medtronic investigated these events collectively as a UADE because of the rate of reported stopped pumps. The current estimated survival probability at 60 months (82.5%) is below the projected survival rate (85.9%).

[b] Green loose stool and abdominal cramping were reported for the same subject 16 days post implant. The site PI and AEAC could not rule out that these symptoms may be related to Remodulin.

Note: An event may be both procedure-related and system-related.

Note: An event may be related to more than 1 procedure or component.

A system-related adverse event is defined as an adverse event related to 1 or more of the system components: the catheter, pump, and programmer. Excluding anticipated adverse events, there were 25 system-related (pump or catheter) adverse events occurring in the study. There were no events deemed related to the programmer. They are summarized in Table 9.

Table 9. Post-implant system-related adverse events

Adverse event preferred term	Number of Events (number of subjects, % of subjects) (n = 60)
Abdominal pain lower	1 (1, 1.67%)
Abdominal pain upper	1 (1, 1.67%)
Contusion	1 (1, 1.67%)
Dermatitis contact	1 (1, 1.67%)
Device battery issue	1 (1, 1.67%)
Device damage	2 (1, 1.67%)
Device dislocation	1 (1, 1.67%)
Device malfunction	3 (3, 5.00%)
Erythema	1 (1, 1.67%)
Implant site extravasation	3 (3, 5.00%)
Lead dislodgement	3 (2, 3.33%)
Medical device pain	3 (3, 5.00%)
Muscle spasms	1 (1, 1.67%)
Pulmonary arterial hypertension	1 (1, 1.67%)
Skin striae	1 (1, 1.67%)
Venous stenosis	1 (1, 1.67%)
Total	**25 (19, 31.67%)**

Among the 60 subjects and excluding anticipated adverse events, there were 1151 adverse events that were not related to the system (catheter, pump, or programmer). Non-system-related adverse events that occurred 5 or more times are listed in Table 10 but some adverse events may have been procedure-related.

Table 10. Post-implant adverse events not related to the system with 5 or more occurrences

Preferred term	Number of events (number of subjects, %) (n = 60)
Upper respiratory tract infection	61 (32, 53.33%)
Implant site pain	45 (43, 71.67%)
Pulmonary arterial hypertension	39 (21, 35.00%)
Dyspnoea	28 (20, 33.33%)
Headache	24 (18, 30.00%)
Injection site reaction	24 (16, 26.67%)
Nasopharyngitis	21 (15, 25.00%)
Immediate post-injection reaction	20 (16, 26.67%)
Fluid overload	18 (8, 13.33%)
Hypotension	18 (15, 25.00%)
Atrial fibrillation	17 (5, 8.33%)
Injection site pain	17 (13, 21.67%)
Pneumonia	17 (13, 21.67%)
Dizziness	16 (14, 23.33%)
Fatigue	15 (14, 23.33%)
Sinusitis	15 (11, 18.33%)
Nausea	14 (13, 21.67%)
Urinary tract infection	14 (9, 15.00%)
Bronchitis	13 (12, 20.00%)
Diarrhoea	13 (11, 18.33%)
Pain in extremity	13 (13, 21.67%)
Hypokalaemia	11 (7, 11.67%)
Implant site bruising	11 (10, 16.67%)
Abdominal pain	9 (9, 15.00%)
Anxiety	9 (8, 13.33%)
Dyspnoea exertional	9 (7, 11.67%)
Flushing	9 (9, 15.00%)
Influenza	9 (8, 13.33%)
Oedema peripheral	9 (7, 11.67%)
Palpitations	9 (6, 10.00%)
Vomiting	9 (9, 15.00%)
Back pain	8 (8, 13.33%)
Rash	8 (6, 10.00%)
Right ventricular failure	8 (7, 11.67%)
Syncope	8 (7, 11.67%)
Musculoskeletal pain	7 (6, 10.00%)
Nasal congestion	7 (5, 8.33%)
Arthralgia	6 (5, 8.33%)
Depression	6 (6, 10.00%)
Gastrointestinal haemorrhage	6 (4, 6.67%)
Haemoptysis	6 (1, 1.67%)
Insomnia	6 (6, 10.00%)
Adverse drug reaction	5 (5, 8.33%)
Atrial tachycardia	5 (3, 5.00%)
Cardiac failure	5 (4, 6.67%)
Chest discomfort	5 (5, 8.33%)
Cough	5 (4, 6.67%)
Ear infection	5 (5, 8.33%)
Fluid retention	5 (4, 6.67%)
Gastrooesophageal reflux disease	5 (5, 8.33%)
Hypoxia	5 (4, 6.67%)
Musculoskeletal chest pain	5 (3, 5.00%)
Neck pain	5 (5, 8.33%)
Supraventricular tachycardia	5 (3, 5.00%)

Refill reactions

Refill reaction is defined as reported adverse events (AEs) that were adjudicated by the AEAC as refill-related, drug-related, and not catheter-related. A refill reaction is caused by subcutaneous leaking of Remodulin from the needle during withdrawal of needle from the reservoir septum at the end of the refill process. The refill reaction can be local, systemic, or systemic and local:

- Local: pain, erythema (redness), and/or swelling near pump/injection site
- Systemic: flushing, headache, nausea and/or hemodynamic changes
- Serious (clinical study/FDA definition) – hospitalization or life threatening event

In the clinical trial, it was demonstrated that chilling drug prior to the refill reduced the incidence and magnitude of the refill reactions. Refilling the pump with cold drug condenses the propellant surrounding the expandable/collapsible pump reservoir causing negative pressure for short duration in the pump reservoir. The negative pressure in the reservoir and refill needle causes drug in the needle to be pulled into the needle/extension tubing during withdrawal of the needle from the reservoir minimizing or eliminating subcutaneous delivery of a droplet of Remodulin. Table 11 summarizes the refill reactions.

Table 11. Summary of refill reactions

Refill reaction	Non-chilled drug refills (n = 1053)	Chilled drug refills (n = 1176)
Local N (%)	21 (2.0%)	9 (0.8%)
Systemic N (%)	8 (0.8%)	5 (0.4%)
Systemic and local N (%)	13 (1.2%)	2 (0.2%)
Total refill reactions N (%)	**42 (4.0%)**	**16 (1.4%)**
Serious n (%)	10 (0.9%)	2 (0.2%)

1.7 Death summary

There have been 14 deaths as of the July 12, 2017 data cut date. These deaths were reviewed by the Adverse Event Advisory Committee (AEAC), and 13 were adjudicated as not related to the investigational system. One death was adjudicated as related to a pump failure. Table 12 summarizes the 14 subject deaths.

Table 12. Summary of subject deaths

Subject	Days after first implant	Cause of death (preferred term)
M100800002	87	Cardiac failure
M100100002	129	Pulmonary embolism
M100100011	299	Right ventricular failure
M100500004	615	Cardiac failure
M100800004	728	Cardiopulmonary failure
M101000005	857	Cardiac arrest
M100600005	888	Respiratory failure
M100100012	995	Haemoptysis
M100800006	1139	Pulmonary arterial hypertension
M101000004	1420	PAH Disease Progression
M100100007	1472	Embolic strokes
M100500007	1525	Hemorrhagic shock
M100900002	1539	Acute on chronic systolic right heart failure
M101000002	1745	Pump failure

1.8 Discontinuation of therapy

Three clinical study subjects had bilateral lung transplants. In all 3 cases prior to the lung transplant, the Remodulin delivery was transitioned to an external delivery system in anticipation of the lung transplant procedure. For the transition to an external delivery system the pump was filled with saline, transitioned by up titration of Remodulin with the external system. When all the Remodulin was out of the implanted system and the implanted pump was programmed to minimal rate. At the time the subjects received a bilateral lung transplant, 2 of the 3 implantable systems were fully explanted.

1.9 System reliability

Data in this section of the report is through July 12, 2017.

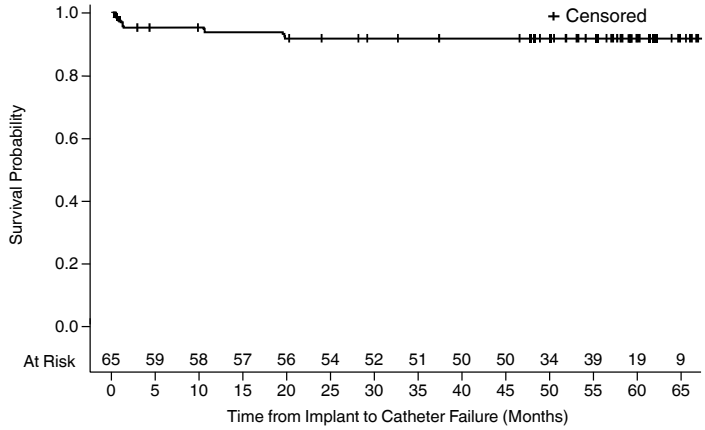
1.9.1 Catheter reliability

Catheter failures include adverse events that required replacement of the catheter. There were 5 events including: 3 catheter dislodgments from the vasculature (key term as lead dislodgment) and 2 subcutaneous leakage of Remodulin due to catheter puncture by needle during refill (key term as injection site reaction). Table 13 summarizes the catheter time from implant survival estimates. Figure 3 is a Kaplan-Meier curve of the data in Table 13.

Table 13. Survival estimates for the event catheter failure

Time from implant to catheter failure (months)	Survival estimate	Survival estimate 95% confidence limits
1	96.9%	(88.2%, 99.2%)
5	95.3%	(86.2%, 98.5%)
10	95.3%	(86.2%, 98.5%)
15	93.7%	(84.0%, 97.6%)
20	92.0%	(81.9%, 96.6%)

Figure 3. Kaplan-Meier curve for event catheter failure



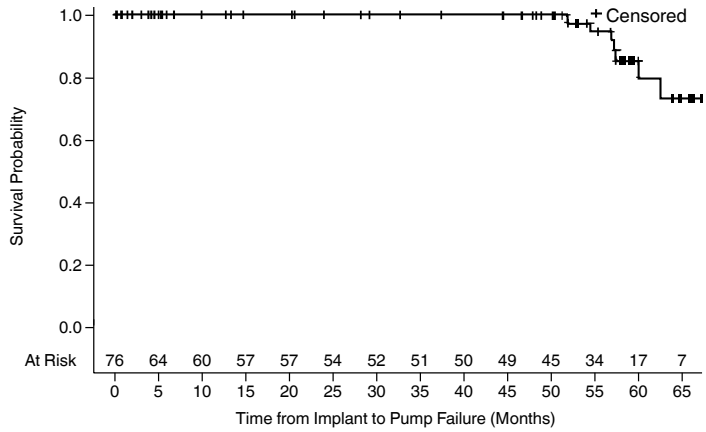
1.9.2 Pump reliability

There were 13 pump replacement events due to all pump causes (pump reaching/nearing elective replacement indicator (ERI), pump failures, or other pump-related reason). Six pumps were replaced for expected ERI, 5 pumps replaced due to pump motor failure, 1 pump replaced due to premature ERI, and 1 replaced for low refill accuracy ratio. ERI will be triggered at 81 months post implant, but will be triggered earlier when the average flow rate is greater than 0.9 mL/day. Table 14 summarizes the pump time from implant survival estimates. Figure 4 is a Kaplan-Meier curve of the data in Table 14

Table 14. Survival estimates for the event pump replacement due to pump cause

Time from implant to pump replacement due to pump cause (months)	Survival estimate	Survival estimate 95% confidence limits
40	100.00%	—
45	98.00%	(86.6%, 99.7%)
50	98.00%	(86.6%, 99.7%)
55	86.1%	(71.5%, 93.5%)
60	74.7%	(57.8%, 85.7%)

Figure 4. Kaplan-Meier curve for event pump replacement due to pump cause



Pump failure is defined to be pump motor stall or premature battery depletion. There were 7 pump failures: 6 due to pump motor stall and 1 due to premature battery ERI. Five of the 6 pumps with motor stall were replaced, and 1 death was adjudicated as related to pump motor stall.

Table 15 summarizes the pump time from implant to pump failure survival estimates. Figure 5 is a Kaplan-Meier curve of the data in Table 15. Table 15 summarized the pump time from implant to pump failure survival estimates. Figure 5 is a Kaplan-Meier curve of the data in Table 15.

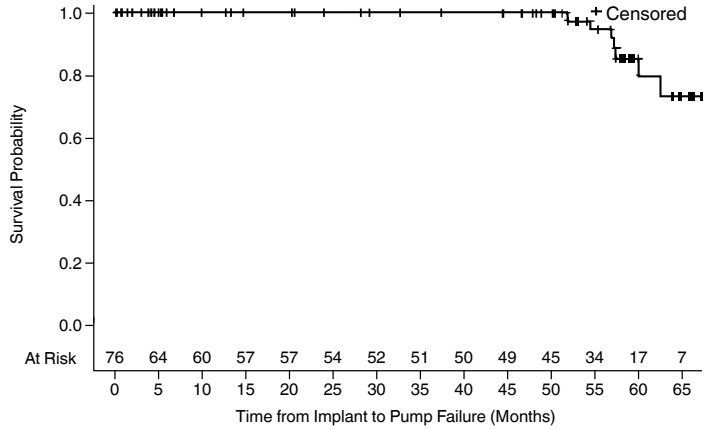
Table 15. Survival estimates for the event pump failure

Time from implant to pump failure (months)	Survival estimate	Survival estimate 95% confidence limits
50	100.00%	—
55	94.7%	(80.4%, 98.7%)

Table 15. Survival estimates for the event pump failure (continued)

Time from implant to pump failure (months)	Survival estimate	Survival estimate 95% confidence limits
60	85.3%	(68.1%, 93.7%)
65	73.3%	(49.4%, 87.2%)

Figure 5. Kaplan-Meier curve for event pump failure



1.10 System performance

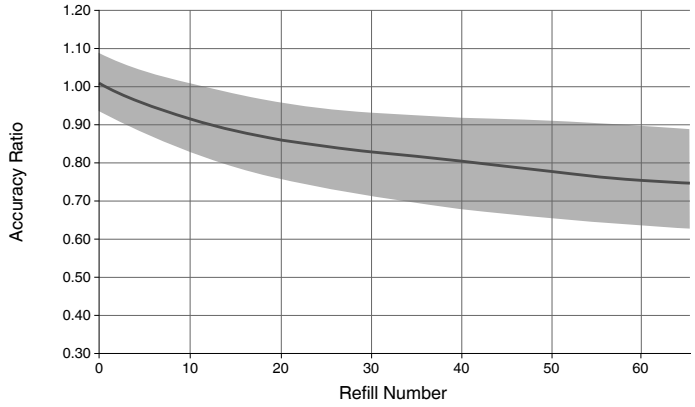
In the DellVery for PAH clinical trial, a trend was seen of more drug removed from the pump at refill than expected (less drug delivered than expected). The ratio of actual versus expected drug delivered at refill (refill accuracy ratio) decreased as the number of refills increased. See Figure 6 for the DellVery for PAH clinical trial flow rate accuracy data (refill accuracy ratio).

Based upon the accuracy ratio data from the study, it has been determined that over a period of time (months to years), the accuracy ratio of the ISR gradually decreases. The decrease is due to an equilibration of gas pressures within the motor chamber. The clinical data, mathematical modeling, and bench testing indicate that over the expected longevity of the pump, the accuracy ratio will decrease and plateau at approximately 0.8. The expected accuracy ratio of the ISR for a 40 mL refill volume is depicted in Figure 7.

Figure 6. Calculation of accuracy ratio

$$\textit{Accuracy Ratio} = \frac{\textit{Previous fill volume - Actual removed volume}}{\textit{Previous fill volume - Expected removed volume}}$$

Figure 7. Implantable System for Remodulin expected accuracy ratio for a 40 mL refill volume. The shaded area represents the DellVery for PAH clinical trial refill accuracy data (95/95% tolerance interval of the exponential data model).



1.11 Clinical study conclusion

A total of 64 subjects were enrolled in the DellVery for PAH study at 10 sites in the United States. Of these, there were 60 attempted system implants and all 60 were successful. There were 5 events that required catheter revisions. There were 7 events that required early pump replacement. This report represents a total of 120.7 years of cumulative follow-up in subjects implanted with the PAH Implantable Vasodilator Therapy system.

The primary safety objective was analyzed with data as of June 13, 2013 and was met ($p<0.0001$). The observed rate of catheter-related complications per 1000 days of 0.27 with the system was significantly less than the rates observed in literature for a CVC system. These rates ranged from 1.05 to 2.51 per 1000 days. Therefore, the safety of the Model 10642 Implantable Intravascular Catheter has been demonstrated.

As expected, efficacy variables including Quality of Life (QoL) (CAMPHOR and EQ-5D questionnaires), 6-Minute Walk, New York Heart Association Functional Classification showed little or no change when comparing the external pump (baseline) to the implanted pump; this was expected since the treatment therapy (Remodulin) is the same with the external and internal pumps.

Overall, the study objectives were met, demonstrating that the Model 10642, when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin, is safe for patients with PAH.

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Medtronic

Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432
USA
www.medtronic.com
+1 763 514 4000

Medtronic USA, Inc.
Toll-free in the USA (24-hour technical consultation for physicians and medical professionals)
Bradycardia: +1 800 505 4636
Tachycardia: +1 800 723 4636

Europe/Middle East/Africa
Medtronic International Trading Sàrl
Route du Molliau 31
Case Postale 84
CH-1131 Tolochenaz
Switzerland
+41 21 802 7000

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