PROMETRA® II

PROMETRA® II 20 ML PROGRAMMABLE PUMP (REF 13827)

PROMETRA® II 40 ML PROGRAMMABLE PUMP (REF 16827)

For use with Intrathecal Catheter

MR Conditional

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

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Introduction

The Prometra II Programmable Pump is designed to provide controlled delivery of drugs to the intrathecal space via the separately supplied Intrathecal Catheter. The Prometra II Pump incorporates a patented flow activated safety valve (FAV™) that will shut off drug flow to the patient in the event that a high flow rate is encountered. The Prometra Programmer is a separately supplied handheld, menu-driven device that enables remote programming of the Prometra II Pump.

Note: The use of the terms “medication” and “drug” throughout this document refer to the use of Infumorph® or baclofen injection (intrathecal).

Contents

The following components are sterile and non-pyrogenic:

- 1 – Prometra II Programmable Pump
- 1 – Needle, Non-Coring, 0.7 mm (22G) x 38 mm (1.5 in.)
- 1 – Needle, Catheter Access, 0.9 mm (20G) x 45 mm (1.75 in.)

Non-sterile components:

- 1 – Patient and Physician Information Packet:
  - 1 – Instructions for Use
  - 1 – Calculations Guide
  - 1 – Patient Guide
  - 2 – Temporary Patient Implant Cards
  - 1 – Sheet of Device ID Stickers
  - 1 – Patient Device Tracking Form
  - 1 – Warranty Card

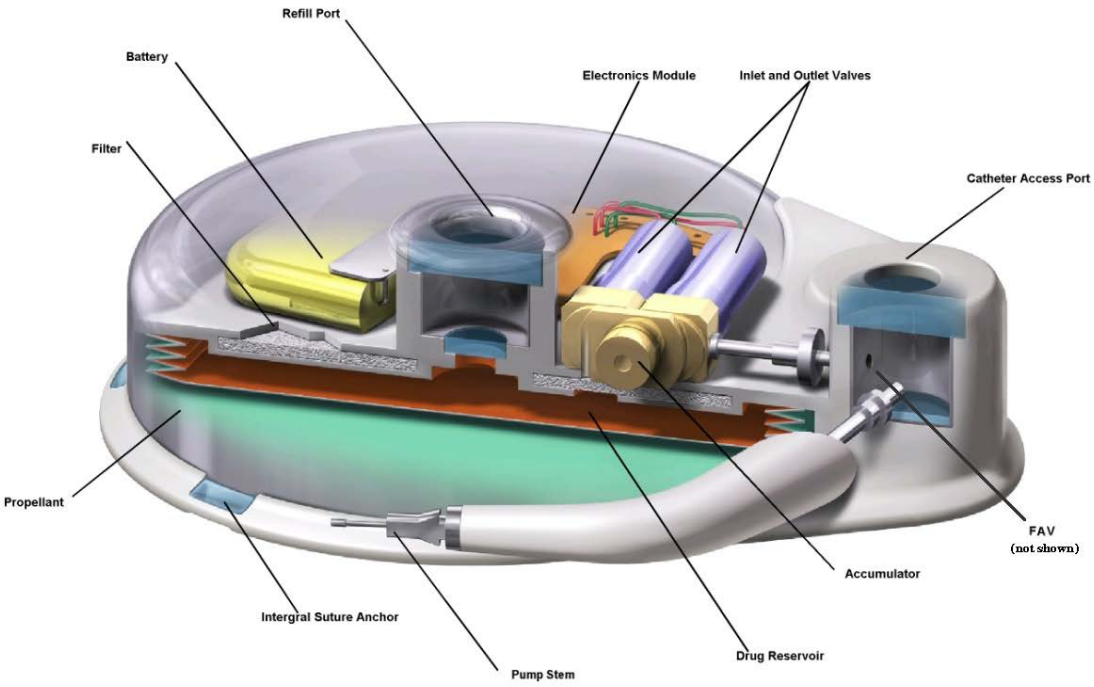
Description

The Prometra II Pump is a battery-powered, teardrop-shaped pump with a rigid titanium housing and a triple redundancy flow controller system. To help increase safety, the Prometra II Pump incorporates a safety valve (flow-activated valve or FAV) that will shut off drug flow to the patient in the event a high flow rate occurs. The Prometra II Pump is available in both 20 mL and 40 mL reservoir capacities.

Prometra II 40 mL Pump

Prometra II 20 mL Pump

The triple redundancy flow control system is designed to provide a precise and accurate flow rate. The flow rate accuracy is independent of normal operating environmental conditions such as altitude, temperature and reservoir volume.



Specifications of the Prometra II Programmable Pump are:

Device Longevity	
Pump	10 years at 0.25 mL/day
Septum (Refill and CAP)	1000 punctures maximum
External Properties	
Material	Titanium Polyphenylsulfone access ports
Thickness (nominal)	20 mm for Prometra II 20 mL (REF 13827) 32 mm for Prometra II 40 mL (REF 16827)
Diameter (excluding CAP)	69 mm
Average Volume Displacement	100 mL for Prometra II 20 mL (REF 13827) 133 mL for Prometra II 40 mL (REF 16827)
Weight, unfilled	150 g for Prometra II 20 mL (REF 13827) 154 g for Prometra II 40 mL (REF 16827)
Drug Reservoir	
Material	Titanium
Usable Capacity	20 mL for Prometra II 20 mL (REF 13827) 40 mL for Prometra II 40 mL (REF 16827)
Precision Dosing System	
Material	Titanium MP35N alloy Stainless steel Silicone rubber
Refill Septum	
Septum material	Silicone rubber
Access needle	Huber point, 22G non-coring needle
Catheter Access Septum	
Septum material	Silicone rubber
Access needle	Lancet point with side hole, 20G
Bacterial filter	
Material	Polyvinylidene fluoride
Pore size	0.22 micron
Flow Rate	
Range	0-28.8 mL/day

Clinical Accuracy	95.9-97.7% (90% confidence limit)
Specified Accuracy	+/-15% for flow rates 0.045–28.8 mL/day
	The accuracy has not been tested and is unknown for flow rates 0 – 0.045 mL/day
Refill Interval	Not more than 90 days for Infumorph® (preservative free morphine sulfate sterile solution), preservative-free sterile 0.9% saline solution (Sodium Chloride Injection, USP) Not more than 60 days for baclofen (baclofen injection, intrathecal, 500-2000 mcg/mL)
Flow Activated Valve (FAV)	
Material	Same as Precision Dosing System
Maximum volume dispersed when closed	10 µl

The Prometra II Pump is supplied with a Catheter Access needle and a non-coring Refill needle for priming the pump at implantation. The Patient Information packet contains a patient guide and two patient implant cards to be completed and given to the patient. Additionally, a federally-mandated patient device tracking form is included and needs to be completed and returned to Flowonix.

Indications

The Prometra® Programmable Infusion Pump System is indicated for intrathecal infusion of drug therapy, including: Infumorph ® (preservative free morphine sulfate sterile solution), preservative-free sterile 0.9% saline solution (Sodium Chloride Injection, USP), and baclofen (baclofen injection, intrathecal, 500-2000 mcg/mL). For Infumorph, the pump system is indicated for use in patient populations of 22 years and older (adults). For baclofen and 0.9% saline solution, the pump system is indicated for use in patient populations of 12 years and older (adolescents and adults).

The approved drug labeling governs the indications, contraindications, warnings and precautions related to the use of the drug.

Drug Information

Refer to the drug labeling for a complete list of indications, contraindications, warnings, precautions, dosage administration information and screening procedures.

Contraindications

Implantation of this device is contraindicated when:

- The presence of infection is known or suspected.
- The patient's body size or anatomy is insufficient to accommodate the size of the implanted pump or catheter.
- The pump cannot be implanted 2.5 cm (1 in.) or less from the surface of the skin. Deeper implants could interfere with septum access or telemetry.
- The patient is known or is suspected to be allergic to materials contained in the catheter: silicone elastomers, barium sulfate, tungsten, polyacetal resin, ink, stainless steel, hydroglide hydro gel coating, or plastic needle hubs (polypropylene and acrylic based).
- The patient is known or is suspected to be allergic to materials contained in the pump: titanium, silicone elastomers, polyphenylsulfone, silicone adhesive, polyvinylidene fluoride, MP35N metal (nickel-cobalt-chromium-molybdenum alloy), or stainless steel (AL29-4, 316L).
- The patient has exhibited a prior intolerance to implanted devices.
- The patient has a spinal column anatomy that would obstruct cerebrospinal fluid flow or that would prevent intraspinal drug administration.
- The patient has emotional, psychiatric or substance abuse problems that are deemed to prohibit intrathecal drug administration.
- Contraindications relating to Infumorph or baclofen injection (intrathecal) must be observed and followed per the approved drug labeling.

Warnings

General

WARNING: USE OF UNAPPROVED DRUGS (e.g., DRUG COCKTAILS, PHARMACY-COMPOUNDED DRUGS, MORPHINE WITH PRESERVATIVES, ETC.) WITH THE PROMETRA II PUMP COULD RESULT IN PUMP FAILURE AND/OR SERIOUS ADVERSE EVENTS SUCH AS SEVERE UNDERDOSE, OVERDOSE OR DEATH.

WARNING: FAILURE TO EMPTY THE PUMP PRIOR TO EXPOSURE TO MRI ENVIRONMENT COULD RESULT IN DRUG OVERDOSE THAT COULD LEAD TO SERIOUS PATIENT INJURY OR DEATH. THE PUMP MAY NEED TO HAVE AS MUCH AS 20ML OR 40ML OF DRUG REMOVED DEPENDING ON THE PUMP TYPE AND MODEL NUMBER.

- Prior to infusion of approved drug into the pump system, medical personnel should be familiar with and observe all warnings, cautions, contraindications, and instructions as specified by the drug manufacturer.
- Patients should not undergo hyperbaric therapy since exposure could result in drug underdose.
- Physicians must be familiar with the drug stability information in the product insert and must understand the dose relationship to drug concentration and pump flow rate before prescribing pump infusion.

- Always select and program drug dosages consistent with the drug labeling to prevent improper drug administration.
- Inform patients of the signs and symptoms of drug under- or overdose, appropriate drug warnings and precautions regarding drug interactions, potential side effects, and signs and symptoms that require medical attention.
- If suspected 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.
- In the event of over-medication, refer to the approved drug labeling for appropriate treatment.
- Clinicians implanting, programming, accessing, or maintaining implanted programmable pumps must comply with the instructions for use. Technical errors may result in a return of underlying symptoms, drug withdrawal symptoms, or clinically significant or fatal overdose.
- The Prometra II Programmable Pump components are supplied sterile and non-pyrogenic. The packages should be examined carefully prior to opening. Do not use the contents if there is any evidence of damage to the package or package seal that could compromise sterility. Do not resterilize contents of any damaged or opened packages.
- After use, this device is a biohazard. Handle and dispose of in accordance with accepted hospital practice and all applicable laws and regulations.
- Do not incinerate or cremate the pump.
- Do not expose the pump to temperatures above 57˚C (134.6˚F) or below 2˚C (35.6˚F).
- The patient has an occupation where he/she would be exposed to high current industrial equipment, powerful magnets or transmitting towers, such as, electricians, electrical engineers or MRI technicians.

Precautions

General

- Carefully read all instructions prior to use. Follow all instructions.
- Certain equipment may cause electrical noise, which may interfere with programming. If suspected, move the patient from the suspected source of interference to facilitate the programming procedure. Examples of equipment that may cause interference include cathode ray tube (CRT) monitors and large electric motors.
- Do not use accessories that are not referenced in these instructions for use. Only use devices and accessories that are referenced for use with the Prometra® II Programmable Pump in these instructions.
- Safety and effectiveness for use in pediatric patients with Infumorph under 22 years old has not been investigated or established.
- Safety and effectiveness for use on pediatric patients with baclofen below the age of 12 has not been investigated or established.
- The effects of implanting this device in patients with other implanted medical devices, other than neurostimulators, are unknown.
- Pain on injection that was not noted during previous injections may be an early sign of infection.

Implant

- Implantation of this device and subsequent use, reprogramming, and refill should only be conducted by qualified medical personnel specifically trained for surgical implantation, use, and maintenance of the device. Use of this device by non-qualified or untrained personnel could lead to serious consequences involving under- or over-medication. In the event of over-dosage, refer to the approved drug labeling for appropriate treatment.
- Monitor patients after pump and/or catheter implant or replacement for signs of underdose/overdose.
- The pump and catheter system should be implanted carefully to avoid any sharp or acute angles, which could compromise the patency of the catheter lumen.
- Over-pressurization can damage the catheter. Small syringes can generate very high pressures and may damage the catheter or catheter connection. Do not use a syringe smaller than 10 mL when accessing the catheter access chamber.
- If therapy is discontinued for an extended period, the pump should be emptied of the drug and filled with a preservative-free 0.9% sterile saline solution and programmed to a low infusion rate to maintain catheter patency.
- In the pediatric population, care must be taken to select an appropriate location, taking into consideration:
    - available body mass,presence of ostomies,growth development, andco-morbidities.

Device Compatibility

- **Pump accessories.** Only use the Prometra II Programmable Pump with the accessories listed in these instructions for use. Use of alternate accessories may result in damage to Prometra II components, less than adequate therapy, or increased risks to the patient.
- **Pump.** Only use with Prometra Programmer.

- **Alcohol.** Do not use alcohol on any part of the pump or catheter system. Alcohol is neurotoxic.
- **Contrast media.** Do not inject contrast media into the refill reservoir since this may damage the pump or impair pump function.
- **External devices.** Do not connect any external devices or pumps to the Prometra II Pump. Pressures generated by an external pump could damage the implanted pump/catheter system and result in serious patient injury or death.
- **Therapeutic ultrasonics or lithotripsy -** Use of therapeutic ultrasonic devices, such as electrohydraulic lithotriptors, has not been tested on the Prometra II pump. If lithotripsy must be used, do not focus the beam in proximity of the pump.
- **Medical devices**. The Prometra Programmer may affect other medical devices. Use or interference with medical devices, other than neurostimulators, has not been established.
- **Applied electric currents.** Interaction of the Prometra II Pump with electric currents applied to the body such as cardioversion or defibrillation has not been established. Care must be exercised if the patient receives these treatments. Where practical, the pump should be turned off before application of electric currents to the patient's body. Confirmation that the pump programming has not changed must be carried out as soon as possible after the procedure.
- **Radiation.** Do not use radiation therapy in the area of the pump. The effects of ionizing radiation on the Prometra II Pump have not been established, and these therapies may have effects on pump operation that are not immediately apparent.

Potential Adverse Events

The potential exists for serious complications including the following:

Possible Risks Associated with Programmable Implantable Pump:

- Adverse reaction to pump materials
- Battery depletion
- Bleeding
- Body rejection phenomena
- Defective pump (e.g. propellant chamber leakage, pump rupture)
- Inability to locate septum
- Inability to program pump due to programmer failure or loss of telemetry
- Inflammation, necrosis, or scarring of skin over implant area
- Potential withdrawal and decreased efficacy due to end of device service life
- Programming errors, resulting in over or under dosing
- Pump flipping or twisting
- Pump implanted too deep, resulting in difficulty accessing or inability to access port
- Pump migration
- Pump pocket pain/soreness
- Pump pocket seroma/hematoma, with or without infection
- Pump rotation
- Pump site skin erosion
- Pump stoppage

- Refill errors, including injection into pump pocket, injection into wrong port, incorrect volume, incorrect concentration, difficulty accessing pump port
- Septum dislodgement
- Septum leakage
- Slow, erratic or fast flow
- Software error

Possible Risks Associated with Intrathecal Catheter:
- Catheter disconnection
- Catheter kinking
- Catheter fracture
- Catheter migration (unrelated to surgical complication)
- Cerebrospinal fluid (CSF) leak
- Disconnection
- Erosion
- Fibrosis
- Infection in intrathecal space, including meningitis
- Inflammatory mass formation (e.g., granuloma)
- Malpositioning
- Nerve damage
- Pain on injection
- Poor radiopacity
- Post dural puncture headache
- Reaction to catheter materials
- Reversible or irreversible partial or complete occlusions
- Spinal cord pressure leading to paralysis
- Spinal cord trauma, perforation, laceration
- Subcutaneous catheter tract infection
- Subcutaneous tunnel infection
- Tears/breaks

In rare instances, the development of an inflammatory mass at the tip of the implanted catheter may occur, which can result in serious neurological impairment. Patients should be monitored carefully at each visit for any new neurological signs or symptoms, including:
- progressive change in the character, quality, or intensity of pain
- an increase in the level and degree of pain despite dose escalation
- sensory changes (i.e., numbness, tingling, burning)
- hyperesthesia and/or hyperalgesia

Presentations that require immediate diagnosis include
- bowel and/or bladder dysfunction
- myelopathy
- conus syndrome
- gait disturbances or difficulty ambulating

- paraparesis or paralysis

If the presence of an inflammatory mass is suspected, recommended evaluation should include a review of the patient history and neurological evaluation, radiological diagnostic procedures (such as a CT scan with contrast) and appropriate clinical consultation.

Inflammatory mass has been associated with a wide range of doses and concentrations of opioids. No dose or concentration of Infumorph can be considered completely free of risk from inflammatory mass. The risk of inflammatory mass occurrence appears to be cumulative over time and increases with higher concentrations and doses of opioids.

Possible Risks Associated with Infumorph injection (intrathecal):

Contraindications:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting in absence of resuscitative equipment
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Hypersensitivity or intolerance to morphine
- Contraindications to the use of neuraxial analgesia include: the presence of infection at the injection microinfusion site, concomitant anticoagulant therapy, uncontrolled bleeding diathesis and the presence of any other concomitant therapy or medical condition which would render epidural or intrathecal administration of medication especially hazardous.

Select Warnings and Precautions:

- Morphine sulfate may be habit forming. Overdoses may cause respiratory depression, coma, and death.
- Chronic Neuraxial opioid analgesia is appropriate only when less invasive means of controlling pain have failed and should only be undertaken by those who are experienced in applying this treatment in a setting where its complications can be adequately managed.
- Because of the risk of severe adverse effects, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial (single) test dose and, as appropriate, for the first several days after catheter implantation.
- The facility must be equipped to resuscitate patients with severe opiate overdosage, and the personnel must be familiar with the use and limitations of specific narcotic antagonists (naloxone, naltrexone) in such cases.
- Reservoir filling must be performed by fully trained and qualified personnel following directions provided in the Pump Instructions for Use.
- Extreme care must be taken to ensure that the needle is properly in the filling port of the device before attempting to refill the reservoir. Injection of the solution into the tissue around the device or attempting to inject the refill dose into the catheter access port may result in a large, clinically significant, overdosage to the patient.
- A period of observation appropriate to the clinical situation should follow each refill or manipulation of the drug reservoir. Before discharge, the patient and attendant(s) should receive proper home care instructions for the device.

- Risk of Inflammatory Masses: Monitor patients receiving continuous infusion of INFUMORPH via indwelling intrathecal catheter for new signs or symptoms of neurologic impairment.
- Risk of Tolerance and Myoclonic Activity: Monitor patients for unusual acceleration of neuraxial morphine, which may cause myoclonic-like spasm of lower extremities. Detoxification may be required.
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration.
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid.
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of INFUMORPH in patients with circulatory shock.
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of INFUMORPH in patients with impaired consciousness or coma.

For more information, refer to the prescribing information of the drug.

Possible Risks Associated with baclofen injection (intrathecal):

Contraindications

- Hypersensitivity to baclofen injection (intrathecal)
- Baclofen injection (intrathecal) is not recommended for intravenous, intramuscular, subcutaneous or epidural administration.

Select Warnings and Precautions

- There are no adequate and well controlled studies in pregnant women.
- Nursing mothers should exercise caution, as oral baclofen injection has been shown to pass milk at therapeutic doses.
- Patients suffering from impaired renal function, autonomic dysreflexia, psychotic disorders, schizophrenia, or confusional states should be carefully evaluated.
- It is mandatory that all patients, caregivers, and treating physicians receive adequate information regarding the risks of baclofen injection (intrathecal). Instruction should be given on signs and symptoms of underdose and overdose, procedures to be followed in the event of an underdose or overdose, and proper home care of the pump and insertion site.
- Due to the possibility of life-threatening CNS depression, cardiovascular collapse, and/or respiratory failure, physicians must be adequately trained and educated in chronic intrathecal infusion therapy.
- Patients should be infection-free prior to both a screening trial and a pump implantation. The presence of infection may interfere with an assessment of the patient's response to bolus baclofen injection (intrathecal), increase the risk of surgical complications and complicate dosing.
- Following pump implantation, and for each adjustment of the dosing rate of the pump and/or concentration of baclofen injection (intrathecal), the patient should be monitored closely.

Prevention of abrupt discontinuation of baclofen injection (intrathecal) requires careful attention to programming and monitoring of the infusion. Early symptoms of under dosing include: return to baseline spasticity, pruritis, hypotension and paresthesias.

Abrupt withdrawal of baclofen injection (intrathecal) may be life-threatening. Symptoms include: high fever, altered mental status, exaggerated rebound spasticity and muscle rigidity. Withdrawal left untreated may result in: rhabdomyolysis, multiple organ failure and death.

Overdosing signs and symptoms include: drowsiness, lightheadedness, dizziness, somnolence, respiratory depression, seizures, rostral progression of hypotonia, loss of consciousness progressing to coma. Should overdose appear likely, the patient should be taken immediately to a hospital for assessment and emptying of pump reservoir.

Baclofen injection (intrathecal) should ordinarily be reduced slowly if the drug is discontinued for any non-emergent reason.

For more information, refer to the prescribing information of the drug.

Clinical Studies

The performance and safety of the Prometra Pump was examined in an open-label, non-randomized, multi-center study. This study was designed to demonstrate the accuracy and safety of the pump's delivery of Infumorph into the intrathecal space.

The primary endpoint of the study was to demonstrate accuracy of drug delivery is within the range of 85-115% through six months post implantation. Additional endpoints evaluated the safety profile, as determined by the rate of device-related serious adverse events and device complications.

A total of 110 Patients enrolled in the study were implanted with the Prometra Pump. Patients eligible for enrollment were suffering from cancer pain requiring strong opioids, chronic, non-malignant pain, or required an implantable pump system replacement due to malfunction or battery depletion. The average patient age at implant was 56 years with 54% male and 46% female patients.

Patients were followed monthly for the first 6 months post implantation. During each monthly follow-up visit, the pump was refilled and infused volumes of medication were documented. Drug delivery accuracy and adverse events were documented at the monthly visits.

Results

The accuracy of drug delivery was found to be 96.8% with a 90% confidence interval of 95.5% - 97.7%. This met the required range of 85% - 115%.

Adverse Events reported during the study are shown in Table 1.

Table 1: Adverse Events Reported as Possibly, Probably, or Definitely Related to the Device or Study Procedure

System Organ Class	Preferred Term	N (%)
Gastrointestinal Disorders	Nausea	15 (14)
	Vomiting	8 (7)
General Disorders and Administration Site Conditions	Implant Site Pain	20 (18)
	Implant Site edema	11 (10)
	Implant Site Erythema	9 (8)
	Implant Site Swelling	4 (4)
	Pain	4 (4)
	Implant Site Inflammation	3 (3)
	Drug Withdrawal Syndrome	2 (2)
	Implant Site Hemorrhage	2 (2)
	Pyrexia	2 (2)
	Tenderness	2 (2)
Infections and Infestations	Incision Site Infection	4 (4)
Injury, Poisoning and Procedural Complications	Procedural Pain	37 (34)
	Post Lumbar Puncture Syndrome	9 (8)
	Wound Secretion	9 (8)
	Seroma	4 (4)
	Wound Dehiscence	3 (3)
Musculoskeletal and Connective Tissue Disorders	Back Pain	2 (2)
	Pain in Extremity	2 (2)
Nervous System Disorders	Headache	8 (7)
	Dizziness	3 (3)
	Intracranial Hypotension	2 (2)
Skin and Subcutaneous Tissue Disorders	Dermatitis Contact	5 (5)
	Pruritus	2 (2)
	Scab	2 (2)
Surgical and Medical Procedures	Surgery[1]	10 (9)

[1] Surgery to replace or revise intrathecal catheter

Adverse Events with incidence of 1% or less. Tinnitus, Abdominal Pain, Constipation, Oral Mucosal Blistering, Catheter Site Edema, Implant Site Bruising, Implant Site Effusion, Implant Site Hypersensitivity, Implant Site Irritation, Implant Site Necrosis, Edema Peripheral, Hypersensitivity, Extradural Abscess, Implant Site Cellulitis, Spinal Infection Viral, Excoriation, Hip Fracture[2], Procedural Nausea, Balance Disorder, Burning Sensation, Diplegia, Hypoesthesia, Neuropathy Peripheral, Tremor, Dyspnea, Respiratory Depression, Ecchymosis, Rash, Hematoma.

[2]Event occurred while patient was being treated with a drug other than Infumorph via Prometra System

Use of Intrathecal Baclofen for Patients 12 – 21 years old (Pediatric Use)

There were no new clinical studies conducted to support the use of the Prometra® Programmable Infusion Pump System with Baclofen in the pediatric adolescent patient sub-population (12 years to 21 years). The safety and effectiveness of the Prometra® Programmable Infusion Pump System for the intrathecal infusion of Baclofen in pediatric patients was based on a systematic review of published peer-reviewed literature that evaluated the reported real world clinical performance of currently available implantable intrathecal drug delivery systems (IDDS) used to deliver Baclofen therapy, and on an analysis of Prometra® Programmable Infusion Pump System performance in adults.

Study Design:

Supporting clinical data for this submission was gleaned from the following process:

- Systematic literature review to support expanding to pediatric subpopulations by drawing from the experience with IDDS in children using ITB therapy.The Prometra® Programmable Infusion Pump System is similar in design, technology, performance, indications for use, output characteristics and patient population to currently available IDDS systems.
- Extrapolation of pump performance from adults to pediatric patients by leveraging data gleaned from adult data using the Prometra® Programmable Infusion Pump Ssytem as well as data gleaned from reports of baclofen therapy (pediatric and adult use) using currently available IDDS systems.
- Leverage use of pump performance (Prometra®) to deliver pain medication in adults to support baclofen delivery to pediatric patients.
- Assess complication rates of the Prometra® Programmable Infusion Pump in adults.
- Leverage historical analysis of post-market pump performance experience, as reported in the literature, with respect to intrathecal delivery

Literature Search Strategy

The objective of the systematic literature search was to identify applicable publications that contain data on the safety and performance of IDDS for treatment of chronic intractable pain and severe spasticity in the adult and pediatric populations.

The scientific literature databases Medline/PubMed and EMBASE were used by the applicant and duplicated by FDA to perform a search for published data relevant to the clinical evaluation of the Prometra® Programmable Infusion Pump System. The search was conducted for literature published January 1, 2000 through January 1, 2021, to gather both background information and relevant data for the use of intrathecal drug delivery systems (IDDS) for the treatment of chronic intractable pain and severe spasticity in adult and pediatric populations. This data obtained from this literature search has been assessed to be acceptable for use in the statistical analysis to identify the similarity and differences in the IDDS complications rates across the adult and pediatric populations. Given there is no information

on adult patients or pediatric patients receiving Baclofen with the Prometra® Programmable Infusion Pump System, inferential statistics were summarized across pump type, population (adult and pediatric), and type of drug administered to quantify the differences. The primary conclusions from the data analysis are as follows:

- In a relatively modest number of patients, there is no significant difference in the reported events and complications ascribed to the pump between adult and pediatric patients receiving baclofen via other commercially available IDDS.
- When comparing relative risk between adult patients receiving baclofen via other commercially available IDDS and pediatric patients receiving baclofen via other commercially available IDDS, results revealed that pump malfunction requiring explant was higher in the pediatric patients compared to the adult patients (2.8% higher in the pediatric patient). However, the overall reported incidence was relatively low, 3.9%
- Across all of the data collected in the literature search the rate of pump malfunctions in the adult population for other commercially available IDDS did not exceed 4.5% and the rate of pump malfunctions in the pediatric population for other commercially available IDDS did not exceed 4%.

Across the range of 25 individual events and complications, there were differences observed between the adult and pediatric patients with the other commercially available IDDS, but these differences were within the expected differences when the underlying etiology of the patients is considered.

Safety and Effectiveness Results

Safety Results

Taken together, the approved adult baclofen infusion indication and the general clinical information on ITB infusion in adult and pediatric populations, as evidenced from the literature can be used to support safety of the Flowonix Prometra® Pump System for the infusion of baclofen in patients down to age 12. FDA analyzed the complication and adverse event rates reported either in peer-reviewed literature or from post-market surveillance for ITB infusion in pediatric patients, as summarized in the Pediatric Extrapolation section below.

Effectiveness Results

FDA determined the Flowonix Prometra® Pump System is comparatively similar to other currently available IDDS, and the submitted published data generated on patients using these other IDDS systems could be extrapolated to provide information generally on intrathecal infusion of Baclofen in pediatric patients. For example, the relevant device design, method of insertion, and programmable aspects of the devices are similar, and the pumps are a similar size and shape.

Pediatric Extrapolation

The Pediatric Extrapolation Decision Tree provided in the *Guidance for Industry and Food and Drug Administration Staff, Leveraging Existing Clinical Data for Extrapolation*

to Pediatric Uses of Medical Devices, issued on June 21, 2016, was used to determine the appropriateness and extent of the extrapolation of clinical data to support a pediatric indication for the Prometra® Programmable Infusion Pump System for the intrathecal infusion Baclofen.

FDA first considered the relevance to the adolescent pediatric population of the clinical information submitted in support of infusion of baclofen in adults using the candidate device. FDA determined there are no relevant differences between adolescent pediatric and adult populations that would require different clinical data with respect to pump insertion, biocompatibility, device performance, or other pump performance parameters. For example, for pediatric patients, the onset, peak response, and duration of action are similar to those seen in adult patients and may vary with individual patients depending on the dose and severity of symptoms[6-10]. In addition, baclofen infusion is currently approved for pediatric patients down to 4 years of age. FDA then considered the expected Similarity of Response to Intervention and quality of data. A summary of these assessments are presented below.

Expected Similarity of Response to Intervention

Question C-1:	*Is the device implanted or in contact with the body, and, if so, does either location or duration of implantation differ between the adult and intended pediatric population in such a way that the safety or effectiveness of the device could be impacted in a clinically meaningful way?*	The device is implanted.
	Does either location or duration of implantation differ between the adult and intended pediatric population in such a way that the safety or effectiveness of the device could be impacted in a clinically meaningful way?	**NO**- The Prometra® Programmable Infusion Pump System is an implantable programmable infusion pump, previously approved for the intrathecal infusion of Baclofen, Infumorph and 0.9% Saline in adults 22 and older. Similar commercially available IDDS have been marketed for use with Baclofen in both the adult and pediatric population. The duration of implantation is the same for adults and the pediatric population[19]. In the pediatric population, care must be taken to select an appropriate pump implant location to accommodate the implantable pump for chronic infusion by taking into consideration available body mass, presence of ostomies, and growth and development[11-16]. To assess the potential difference in the safety and performance of the IDDS in the adult and pediatric population, an intra-study summary and comparison of the rate of complications reported in adult and pediatric patients receiving Baclofen with other commercially available IDDS is provided from a retrospective review[18] and a post-market registry[23].

		The complication rates for the "Pump Malfunction Requiring Explant" and "Reposition Pump" are 1% higher in the adult population and "Pump Rotation or Flipping, Subsidence or Movement is 1.7% higher in the pediatric population. Although there are differences seen in the reported complication rates for the pump between the adult and pediatric population, these differences are not statistically different because the 95% confidence limits of the difference included zero. The differences are not considered to be clinically different with no demonstrative impact on the safety to the patient or performance of the pump. To access the potential difference in incidence of pump revisions/post-implantation pump revision between the adult and pediatric the results from a post-market registry[23] for other currently available IDDS were analyzed. The proportion of adult and pediatric patents experiencing the event of interest (intervention following initial implantation) was compared for each 1-year interval following initial implantation. The results indicate that the incidence of intervention was significantly greater in the pediatric patients 1-2 years and 6-7 years post implantation. The author indicates that the risk of surgical revision (number of interventions/ITB naïve patients followed) is highest (adult: 0.112, pediatric: 0.134, cumulative: 0.117) in the first-year post-implant and then rises again in years of anticipated pump replacement. In nonimplant years, surgical revision rates remain low (adult: 0.060, pediatric: 0.073, cumulative: 0.063) relative to published rates and stable. This study had more adult than pediatric spasticity patient, possibility impacting the data. However, after 10 years, 87.2% of the adult and 76.3% of the pediatric patients continued with ITB. The Prometra® Programmable Infusion Pump results were contrasted against the adult and pediatric results presented above. Reported results for implantation during the first year for 738 adult patients and 224 pediatric patients was 11.2% and 13.4%, respectively. Results during the 5th year of implantation revealed an intervention incidence of 6.6% in 332 patients. Comparable results over a similar time frame with the Prometra® Programmable Infusion Pump revealed that the incidence of revisions was 1.2% (24/1,995). Over the 7.5 years of implantation of the Prometra® Programmable Infusion Pump, from 2013 through the middle of 2020, the incidence of revisions within the first year of implantation has dropped from 4.35% (5/115) in 2013 to 0.40% (6/1,494) in 2020. In aggregate, the total incidence of revisions with the Prometra® Programmable Infusion pump has been 6.58% (611/9,288) suggesting that the Prometra®

		Programmable Infusion Pump should have comparable incidences of revisions in both the adult and pediatric population as reported for other commercially available IDDS.
Question C-2:	*Are there differences in device characteristics between pediatric and adult use that could impact either device safety or effectiveness in the pediatric population in a clinically meaningful way?*	**NO**- The patient evaluation, pump implantation and therapy maintenance are the same for adults and the pediatric population.
Question C-3:	*Are there characteristics unique to the intended pediatric population that could impact either the effectiveness or safety of the device when used in the pediatric population in a clinically meaningful way?*	**NO-** There are differences in body habitus, subcutaneous tissue and muscle volume and over-size between the adult and pediatric severe spasticity population. In addition, this pediatric population typically suffer co-morbidities including depending on a ventriculoperitoneal (VP) shunt, malnutrition, feeding gastrotomy and severe scoliotic deformities requiring fusion and hardware. These differences have been linked to the higher rate of complications related to the catheter[18]. Comparison of the catheter-related complication rates for other currently available IDDS in the adult and pediatric population revealed that catheter migration, breakage/disruption of the catheter, catheter occlusion, spillage at the time of pull-out, CSF leak/fistula and catheter reposition/advancement were all significantly higher in the patient population. In addition, wound complications (CSF fistula, pseudomeningocele, wound dehiscence, infection) were higher in other currently available IDDS pediatric population when compared to the adult population. The pediatric population is more susceptible to these types of complications due to the decreased amount of muscle and subcutaneous tissue to resist pseudomeningocele formation and wound breakdown[18]. Although there are differences in characteristics unique to the pediatric population with severe spasticity and have been related in increased complication rates related to the catheter and increased wound complications, these events are easily treated, and sequelae is rare. In addition, the benefit of ITB in the pediatric population has been shown to greatly outweigh the risk and negate any clinically meaningful differences[18]. In conclusion, the differences in characteristics unique to the pediatric population does not impact the effectiveness or safety of the device when used in this population in clinically meaningful way.
Question C-4:	*Are there differences in disease characteristics between adult and*	**NO-** Severe spasticity is a conditional that can be caused by many different etiologies (e.g., spinal cords injury, multiple sclerosis, cerebral palsy, traumatic brain injury) and some

	pediatric populations that could impact either device safety or effectiveness in the pediatric populations in a clinically meaningful way	etiologies may be more prevalent in either population. However, the characteristics of severe spasticity do not differ between the adult and pediatric population. IDDS is a specialized neurosurgical treatment provided to either adult and/or pediatric patients to provide continuous ITB infusion to decrease spasticity. For both populations, the treatment is focused on improving range of motion, facilitating movement, reducing the risk of contracture development and improving quality of life.
Question C-5:	*Are there other differences between adult and pediatric populations that could impact either device effectiveness or safety in the pediatric population in a clinically meaningful way?*	**NO-** The differences between the between the adult and pediatric population identified in C1 – C4 are the only differences that have been identified in the literature.

Data Quality

Question:	*Are the adult data of sufficient quality such that they can serve as a substitute for pediatric data to demonstrate safety or effectiveness?*	**YES-** Three sources of high-quality data was used to support the Prometra ® Programmable Infusion Pump System's pediatric indication for Baclofen: 1. Post-market surveillance data for the Prometra® Programmable Infusion Pump for adult pain management over the last five (5) years. 2. Adult and pediatric (ITB) data from peer-reviewed literature. 3. Prometra® Programmable Infusion Pump clinical performance for the infusion of intrathecal morphine sulfate (Infumorph) in the adult population.

Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The assessment of safety was supported by the PUMP1 study (NCT00817596), which was an IDE study conducted by for study of a different indication but using the same device, was leveraged by FDA in this application for the assessment of safety, and included 15 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The assessment of effectiveness was supported by the articles identified in the References section below (Section XVI.) These sources were either randomized controlled trials, or a peer-reviewed analysis of publicly available post-market data, which in general, are considered to have minimal bias, and support the reliability of the data collected. It is for these reasons that we believe that none of the clinical investigators had disclosable financial interests/arrangements as defined in sections

54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

Equipment

- Prometra II Programmable Pump
- Intrathecal Catheter
- Tunneler
- Prometra Programmer (Not Sterile)

The following items may be needed and are not provided:

- Sterile Programmer Sleeve
- Sterile preservative-free 0.9% saline
- Drug solution (infusate) for refill, not to exceed 20 mL for Prometra II 20 mL pumps and not to exceed 40 mL for Prometra II 40 mL pumps.

Pump Operation

Programmable Features

The Prometra Programmer uses telemetry to exchange information with the pump. This information includes the following:

- Date and Time
- Current Prescription
- Patient Identification
- Drug Name and Concentration
- Flow Mode, Drug Dose and Delivery Rate
- Pump Model and Serial Number
- Low Reservoir Setting and Alarm
- Low Battery Alarm
- Next Refill Date

The Prometra Programmer allows clinicians convenient, non-invasive access for interrogating and programming the implanted Prometra II Pump. Refer to the Prometra Programmer Technical Manual for further information regarding pump programming.

- **Note: See tables below for information on Pump Model Compatibility with Clinician Programmer and PTC Software Versions and "Pump Model" Information Displayed on Inquiry Screen for Clinician Programmer Software Versions. Contact Flowonix Technical Solutions at 855-356-9665 if you require access to a Flowonix Clinician Programmer or PTC with upgraded software.**

Pump Compatibility with Clinician Programmer and PTC Software Versions				
	Clinician Programmer software version 2.01.5 and higher	Clinician Programmer software versions 1.02.1, 1.03.2, 1.04.10, 2.00.29, 2.00.30	PTC software version 2.01.1 and higher	PTC software versions 1.00, 1.02, 2.00.10
Prometra 20 mL (REF 11827	✓	✓	✓	✓
Prometra II 20mL (REF 13827)	✓	✓	✓	✓
Prometra II 40 mL (REF 16827)	✓	Not compatible, programmer displays "Communication Failed. Please try again"	✓	Not compatible, PTC displays "Bolus not delivered. Contact physician for pump refill. "

"Pump Model" Information Displayed on Inquiry Screen for Clinician Programmer Software Versions		
	Clinician Programmer software version 2.01.5 and higher	Clinician Programmer software versions 1.02.1, 1.03.2, 1.04.10, 2.00.29, 2.00.30
Prometra 20 mL (REF 11827	Prometra 20 mL	Prometra
Prometra II 20 mL (REF 13827)	Prometra II 20 mL	Prometra II
Prometra II 40 mL (REF 16827)	Prometra II 40 mL	Programmer displays "Communication Failed. Please try again." The Inquiry Screen is not displayed.

Programming Medication Regimens

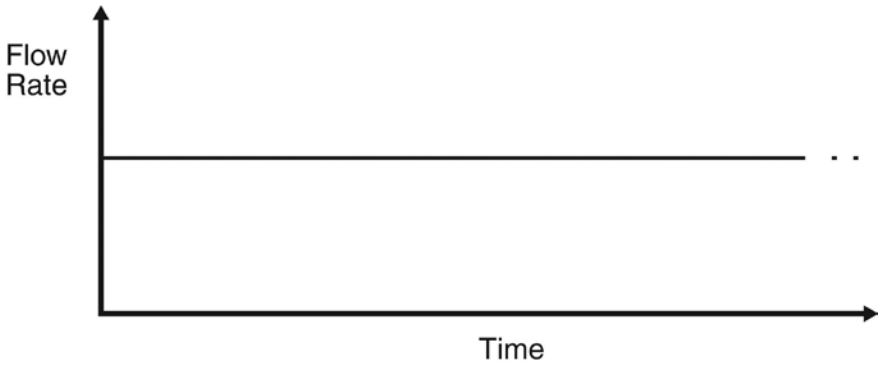
The Prometra II Programmable Pump can be programmed to deliver a precise flow of medication at a constant or variable rate, or it can be set to periodically deliver a drug dosage at distinct intervals of time (i.e. Periodic Flow Mode). There is also an option to interrupt the pump's current medication regimen and deliver an immediate infusion of medication (Demand Bolus). Refer to the Prometra Programmer Technical Manual for further information regarding pump programming.

Warning: Implantation of the Prometra II Programmable Pump System and subsequent use, reprogramming and refill should only be conducted by qualified medical personnel specifically trained for surgical implantation, use and maintenance of the device. Prescription of pump infusion regimens may only be conducted by physicians with a full understanding of the relationships between concentration, dose, and infusion rate. Use of this device by non-qualified or untrained personnel could lead to serious consequences involving under or over-medication. In the event of over-medication, refer to the approved drug labeling for appropriate treatment.

The following illustrations describe the four basic medication regimens:

Constant Flow

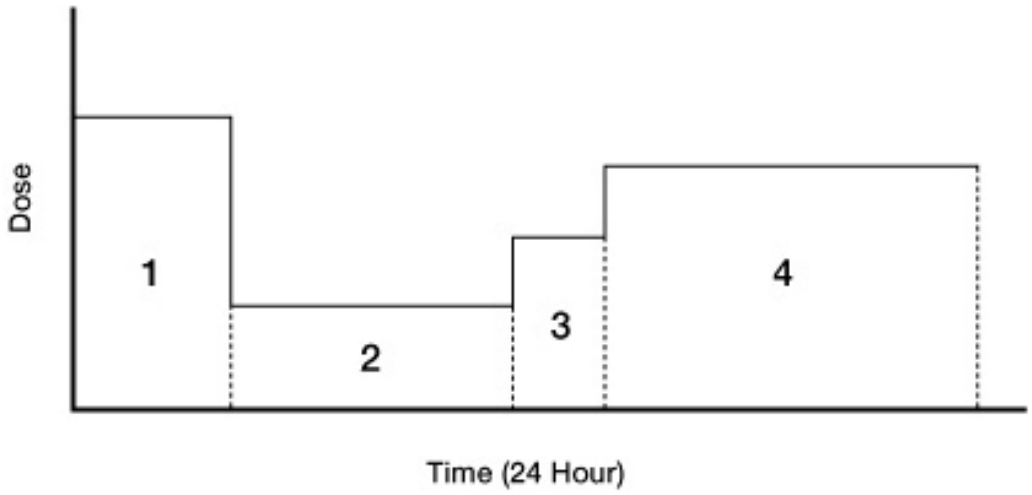
The Constant Flow regimen delivers a specific daily dose, e.g. mg/24 hr, of drug at a constant flow rate dependent on its concentration.



Constant Flow Regimen

Multiple Rates

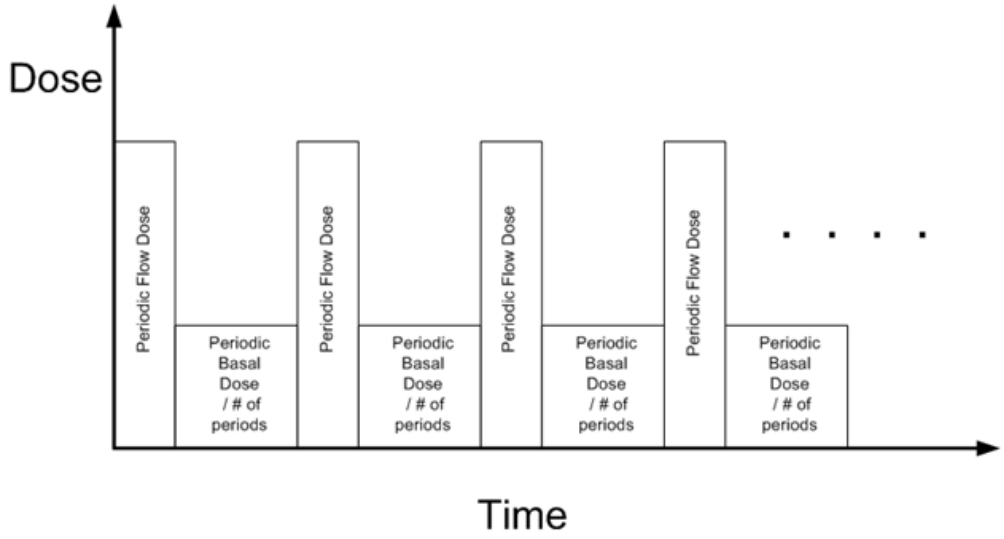
The Multiple Rates regimen delivers medication using one to four user-programmed rates that repeat daily. For each prescribed rate, the specific medication dose and time period is programmed.



Multiple Rates Regimen

Periodic Flow

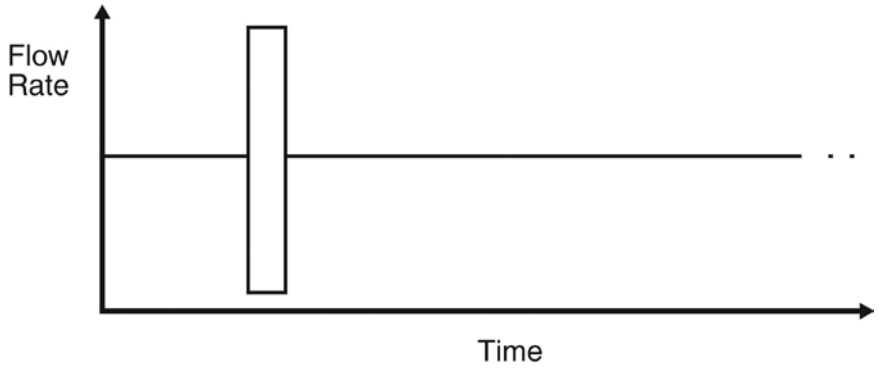
The Periodic Flow regimen delivers medication in a sequence of periodic infusions with a daily basal dose. The first periodic flow dose starts immediately upon programming. When the periodic infusion is not active, medication will be delivered according to the daily basal dose setting. The medication dose, the time over which the dose is delivered, and the interval at which the dose is repeated are programmed.



Periodic Flow Regimen

Demand Bolus

The Demand Bolus regimen temporarily replaces the current dose regimen to deliver an immediate, one-time infusion of medication. The medication dose and the time over which the dosage is delivered are programmed. Once the Demand Bolus is complete, the pump resumes its previously programmed regimen.



Demand Bolus Regimen

Pre-Programmed Pump Settings

When the Prometra Programmer inquires the Prometra II Pump for the first time, the pump status screens display the pre-programmed pump settings. The clinician can change these presets using the programmer.

Parameter	Description	Data Preset
Patient	Name or code	No
Pump Model	Model of Pump	Yes, Prometra II 20 mL or Prometra II 40 mL
Pump SN	Serial Number of Pump (e.g., 36DA4A77)	Yes, pump specific
Pump Ver.	Current pump software version (e.g. 0.29)	Yes, pump specific
Drug	Drug contained in pump	No, specified by user
Conc	Concentration of drug in pump	Yes, preset to 1.000 mg/mL
Accum	Accumulator Volume Constant (e.g. 2.010 µL)	Yes, pump specific
Reservoir Volume	Current estimated volume contained in reservoir	Yes, 00.0 mL
Low Res. Alarm	Alarm to indicate reservoir volume is low	Yes, to OFF
Low Res. Volume	Setting to actuate Low Reservoir Alarm	Yes, 2.0 mL
Battery	Pump battery charge status	No, reports condition, e.g. OK or Low

Parameter	Description	Data Preset
Flow Mode	Constant Flow, Multiple Rates, Periodic Flow or Demand Bolus	Yes, to Constant Flow
Next Refill	Date: month/day/year (mo/da/yr) Calculated by programmer, appears after refill is programmed	No
Daily Dose	Programmed daily dose (e.g. 2.005 mg)	Yes, to 0.000 mg

Pump Alarms

The Prometra II Pump has two audible alarms that alert patients and clinicians to low reservoir volume and critical errors that cause the drug delivery to stop. All alarms use the same tone but can be distinguished from each other by the number of "beeps" in a group and the length of each beep.

Low Reservoir Alarm

The Low Reservoir Alarm warns patients when the medication in the pump reservoir gets below a certain volume. The pump signals a low volume condition by sounding two short (1/4 second) beeps every 30 minutes. The alarm continues to sound until turned off by telemetry using the Prometra Programmer or until a new volume of drug is programmed into the pump.

The Low Reservoir Alarm must be turned "On" and the threshold volume programmed using the Prometra Programmer. When pumps are shipped from the factory, the Low Reservoir Alarm is set to "Off". For information on setting the low reservoir volume and enabling the alarm, refer to the Prometra Programmer Instructions.

Critical Error Alarm

The Critical Error Alarm alerts patients and clinicians that the pump has stopped delivering medication. The pump signals an error condition by sounding three long (1/2 second) beeps every 30 minutes. This alarm occurs for any detected condition that results in the pump not delivering medication, including a low pump battery.

If due to a low battery, the alarm will continue to sound until the pump is explanted or until the battery power is depleted to a point that the pump can no longer communicate with the programmer. As the battery is further depleted, the alarm signal may convert to a continuous tone. If due to another error condition, the alarm continues to sound until a drug delivery schedule is programmed using the Prometra Programmer.

Each time the pump is inquired, the Prometra Programmer reads and displays the condition(s) causing the alarm to sound. The Prometra Programmer clears the error and attempts to restart the pump. If the error condition remains, the pump will restart the error alarm.

Implantation Instructions

The implanting physician is responsible for choosing the surgical procedure, techniques, and the intended therapy for the patient. These instructions are provided as a guide.

Pre-Implant Pump Programming Set Up

Warning: Examine all packages carefully. If any package has been damaged or opened prior to use, do not use package contents. If the pump has been dropped onto a hard surface or shows signs of damage, do not implant. Do not re-sterilize any pump system components.

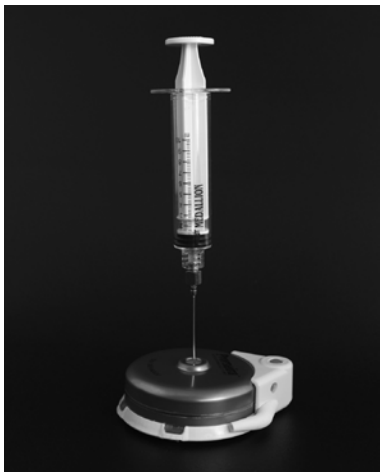
Warning: Make sure the Programmer is sealed in a Sterile Sleeve before approaching the sterile field.

1. Open the outer pump box and verify that the pump serial number on the pump matches that on the Patient Implant Card.
2. Place one of the pump labels on the patient implant card.
3. While the pump is still in the packaging and facing upward, turn the programmer on, press inquire and place the programmer over the pump.
4. From the Main Menu select Setup, Pump Setup, and then Patient Name.
5. Enter the patient's name using the select and navigation keys.
6. Transfer patient's name by placing the programmer over the pump.
7. Under Pump Setup, select low reservoir alarm and program the low reservoir alarm to the "ON" position at a level of 2.0 mL.
8. Verify that the daily dose limit is NOT enabled.
9. Program by placing the programmer over the pump while still in the inner box.
10. From the main menu select refill and enter appropriate refill information (drug name and volume ONLY). Verify the concentration is 1 mg/mL.
11. Remove the pump from the package and pass the pump, catheter, and tunneler to the scrub nurse in sterile fashion.

Pump Priming Preparation

Warning: Extreme caution must be used when filling a Prometra implantable pump, following strict aseptic technique and ensuring fill is directly into the reservoir and not the catheter access port.

1. Attach a sterile syringe filled with 5 mL of sterile preservative-free 0.9% saline solution to the 22G non-coring needle provided in the Prometra II Pump tray.
2. Advance needle through center refill septum until needle tip resides completely inside the drug refill reservoir.



Caution: Do not force the needle. Excessive force on the needle may damage the needle tip. Do not rock the needle sideways as this could damage the septum or cause drug to leak from the reservoir.

3. Inject the 5 mL of sterile preservative-free 0.9% saline solution into the drug reservoir. Allow the saline solution to return from the pump reservoir into the empty syringe barrel. (ensure that all air is removed, if a plunger is present it may prevent all air from being expelled)
   Note: Return volume may be more or less than the infused volume. If air is noted, repeat the priming procedure with another 5 mL of the sterile preservative-free 0.9% saline solution.
4. Remove the syringe from the needle.
   Note: Since some sterile saline will remain in the pump reservoir, the final concentration of drug varies based on the fill method. See the below table for the expected reduction in concentration.

Expected concentration of drug in pump reservoir based on fill method for Prometra II 20 mL

Filling without rinsing	Rinsing with 20 mL of drug
87%	98%

Expected concentration of drug in pump reservoir based on fill method for Prometra II 40 mL

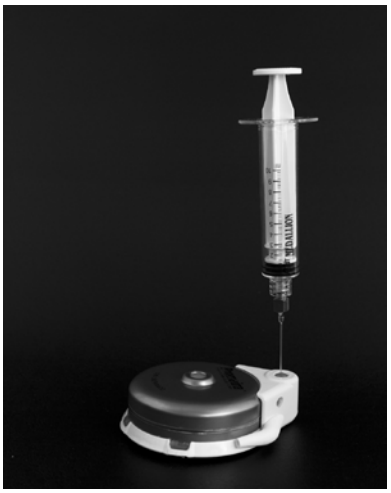
Filling without rinsing	Rinsing with 20 mL of drug
93%	99%

5. If rinsing the pump before filling, rinse and discard the returned volume based on the fill method shown above.
6. For Prometra II 40 mL pumps, two syringes filled with up to 20 mL may be necessary. **Steps 6 and 7** will be completed for each syringe. Verify that the volume of infusate in the syringe(s)

does not exceed 20 mL. Attach the syringe filled with the infusate to the 22G non-coring needle provided with the pump.

Caution: When first filled, the Prometra II Pump has a small amount (2-3ml) of sterile water in the pump. As a result, there is an approximate 13% dilution of drug in the initial filling of the 20mL drug reservoir and an approximate 7% dilution of drug in the initial filling of the 40 mL drug reservoir.

7. Inject the infusate into the pump reservoir. Remove the needle and syringe assembly from the refill septum.
8. For Prometra II 40 mL pumps, repeat **Steps 6 and 7** with the second syringe to fill the pump with another 20 mL of infusate.
9. Remove and discard the knotted silicone rubber tubing from the pump stem.
10. Attach a syringe filled with 5 mL of sterile preservative free 0.9% saline to the 20G Catheter Access Port needle. Advance needle through the Catheter Access septum until needle tip resides completely inside the Catheter Access chamber.



Pump Priming

Warning: Extreme caution must be used when filling a Prometra implantable pump, following strict aseptic technique and ensuring fill is directly into the reservoir and not the catheter access port.

Standard Priming Technique

1. Flush 3mL of the 5ml slowly through the Catheter Access septum to remove air from the fluid pathway. Remove the needle and syringe assembly from the Catheter Access chamber and discard.
2. Obtain a 1 L bag of heated (35-40°C) sterile saline.
3. Program 0.3 mg over a 16 minute demand bolus and immediately submerge the pump in the heated sterile saline bath.
4. After 11 minutes have elapsed, remove the pump from the saline and place on the sterile table.
5. Observe the pump for the remaining 5 minutes, fluid should be expelling from the pump stem every 8 seconds (could be observed as rhythmic spurting or growing fluid bead).

Warning: Please note that the bolus must be completed or if not completed, canceled prior to attaching pump to catheter to avoid medication advancement into the catheter. Do not cancel prior to 11 minutes to ensure fluid pathway is fully primed.

6. If fluid is not observed after following these steps, perform the "Alternate Priming Technique"
7. If fluid is not observed after performing the "Alternate Priming Technique" call Customer Care department for further instructions **855-356-9665.**

Alternate Priming Technique

1. If not already performed, flush 3mL of the 5ml slowly through the Catheter Access septum to remove air from the fluid pathway. Remove the needle and syringe assembly from the Catheter Access chamber and discard.
2. Open a Prometra Refill kit, and using sterile scissors (or sterile blade) cut off one end of the extension set then remove and discard the clip.
3. Attach the cut end of the modified extension set tubing to the pump stem.
4. Retrieve 1 L pre-warmed sterile saline from the incubator.
5. Program a 0.3 mg over 16 minute demand bolus and immediately submerge the pump and modified extension set tubing in the heated sterile saline bath.
6. Confirm that fluid in the extension set tubing is advancing approximately 2-5mm every 8 seconds with the actuation of the valves. Ensure that the fluid movement is pulsatile and not due to thermal expansion.
7. If fluid is not observed after performing the "Alternate Priming Technique" call Customer Care department for further instructions **855-356-9665**.

Warning: Please note that the bolus must be completed or if not completed, canceled prior to attaching pump to catheter to avoid medication advancement into the catheter. Do not cancel prior to 11 minutes to ensure fluid pathway is fully primed.

Implantation of the Intrathecal Catheter

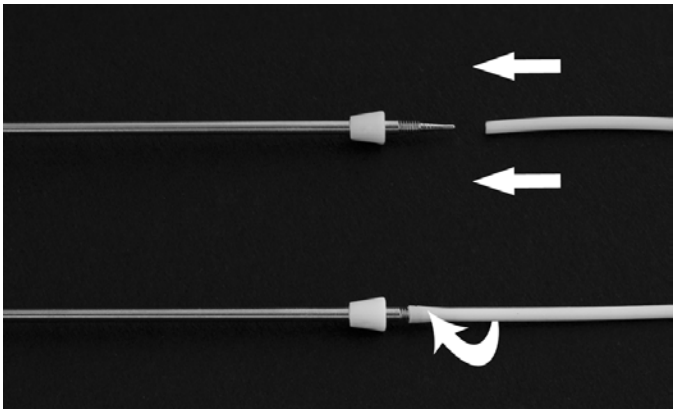
1. **Implant the Intrathecal Catheter as per the Prometra Programmable Infusions Systems Intrathecal Catheter IFU**.

Implantation of the Prometra II Programmable Pump

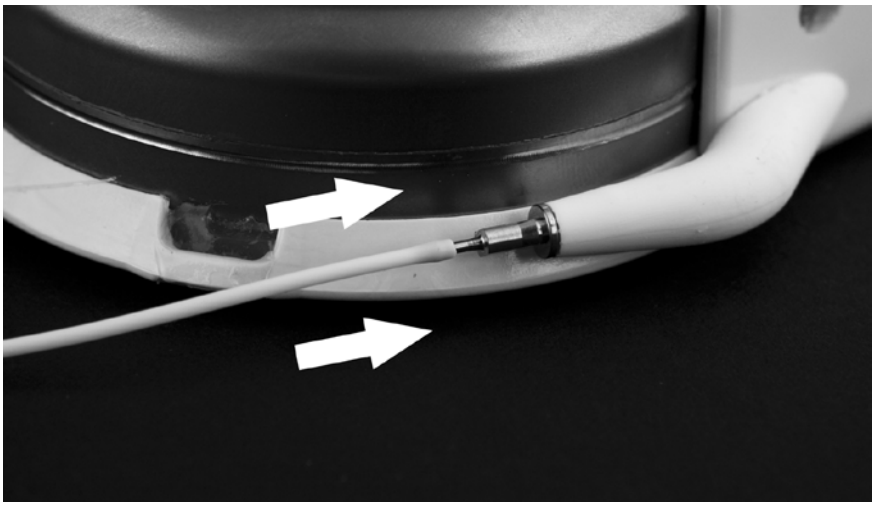
1. **USE STERILE TECHNIQUE**. Always inspect and aseptically prepare the site according to standard practice.
2. Form a subcutaneous pocket using standard technique ensuring snug fit for the pump. Do a trial placement to verify that the pocket is large enough to accommodate the pump and that the pump does not lie beneath the incision.

Warning: Implant the pump 2.5 cm (1 in.) or less under the skin. Deeper implants could interfere with septum access or programming.

3. Create a subcutaneous tunnel using the Tunneler.
4. Push the catheter onto the tunneler until it stops, then turn catheter clockwise until it is fully threaded onto the tunneler.

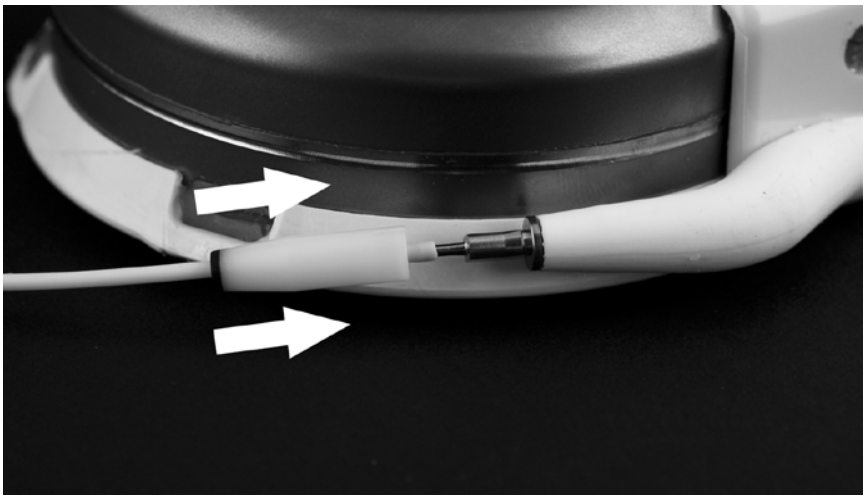


5. Insert the tunneler at the paravertebral incision site and advance the tunneler tip to the pump pocket site. If necessary, use a second tunneling procedure with a temporary exit in the plane of the midaxillary line.
   Warning: Do not puncture the skin or thoracic wall with the tip of the tunneler.
6. Trim the catheter to length at a 90˚ angle allowing sufficient slack for body movement, pump connection, and an additional 2-3 cm in case a pump reconnection is required. Always trim at least 5 cm from the proximal end of the catheter. Assure that the cut is straight and no catheter fragments are produced. Save the trimmed portion of the catheter – the measurement of this piece will be used to calculate the catheter implant volume.
   Caution: Trim excess catheter length, allowing for sufficient length for potential growth. Failure to trim excess length may result in catheter occlusion or kinking.
   Warning: Always save trimmed portion of catheter to measure length and calculate implanted catheter volume. This calculation is required to prevent under- or over-medication.
7. Slide catheter lock on to catheter with larger end towards the pump. Align pump stem with catheter lumen. Advance catheter over barb on pump stem to midway point.



Warning: Prior to advancing the catheter lock, ensure that the catheter is properly positioned on the pump stem. The catheter must be straight with no sign of kinking prior to advancing the catheter lock. A slight pull on the catheter is sufficient to straighten it. Advancing the catheter lock over a kinked catheter may damage the catheter.

8. Advance the catheter lock until it clicks into place, ensuring that the radiopaque band is distal to the pump.



9. Once the catheter and lock are connected, if disconnection and reconnection are required, trim 2-3 cm of the catheter end to ensure a secure connection.
   Caution: Always cut the catheter as close to the pump stem as possible to avoid excessive stretching. Excessive stretching may damage the catheter.
10. Place the pump in the subcutaneous pocket away from the incision line about 2.5 cm (1 in.) beneath the skin surface. The pump should be positioned so that the Catheter Access septum is medial. This allows the catheter a direct line to the spine and keeps this area away from the ribs.
11. Secure to the underlying fascia using one non-absorbable, monofilament suture per pump suture hole. This will reduce the risk of pump migration and the possibility of the pump rotating or flipping over.
12. Verify that the catheter is not kinked or constrained by the pump sutures.
13. After suturing the pump in the pocket, flush the wound with an appropriate antibiotic solution.
14. Close the incision site so that the pump does not lie beneath the incision.
15. Flush the paravertebral site with an appropriate antibiotic solution.
16. Close the entry site making sure the catheter remains straight.
17. Measure and record in the patient's records the length of intrathecal catheter that was trimmed off. This measurement is required to determine the volume of the implanted catheter.
18. Calculate and record the implanted catheter length and volume:

    Implanted Catheter Length (cm) = 110 cm – Trimmed Catheter Length (cm)
    Implanted Catheter Volume (mL) = Implanted Catheter Length (cm) x 0.0026 mL/cm

Warning: Always measure and record the length of the trimmed portion of the catheter, and calculate and record the implanted catheter length and volume. These calculations are required to prevent under- or over-medication.

19. Program the implanted catheter information and drug concentration.
    Warning: The patient should be monitored closely following pump implantation.

Patient Implant Card and Registration

Included with each Prometra II Programmable Pump package is a Patient Implant Tracking/Registration Form. This pre-addressed form should be completed and returned to Flowonix Medical. Flowonix Medical will use this information to create a record of the implant in their database. A copy should also be placed in the patient's implant records.

A patient guide and two patient implant cards are also provided for the patient. The patient implant card contains information pertinent to the implanted Prometra II Programmable Pump. The implant card should be carried by the patient at all times. A second card is provided for placement in their glove box, to be given to a caregiver, or other easily accessible location.

Pump Explantation

The Prometra II Programmable Pump should only be explanted in accordance with the hospital procedures. Explanted product is to be treated as a biohazard.
Warning: Prior to cremation, the pump should always be explanted. The pump will explode at high temperatures.

Calculations

Please refer to the supplementary **Prometra II Calculations Guide**.

Patient-Related Variables and Flow Rate Accuracy

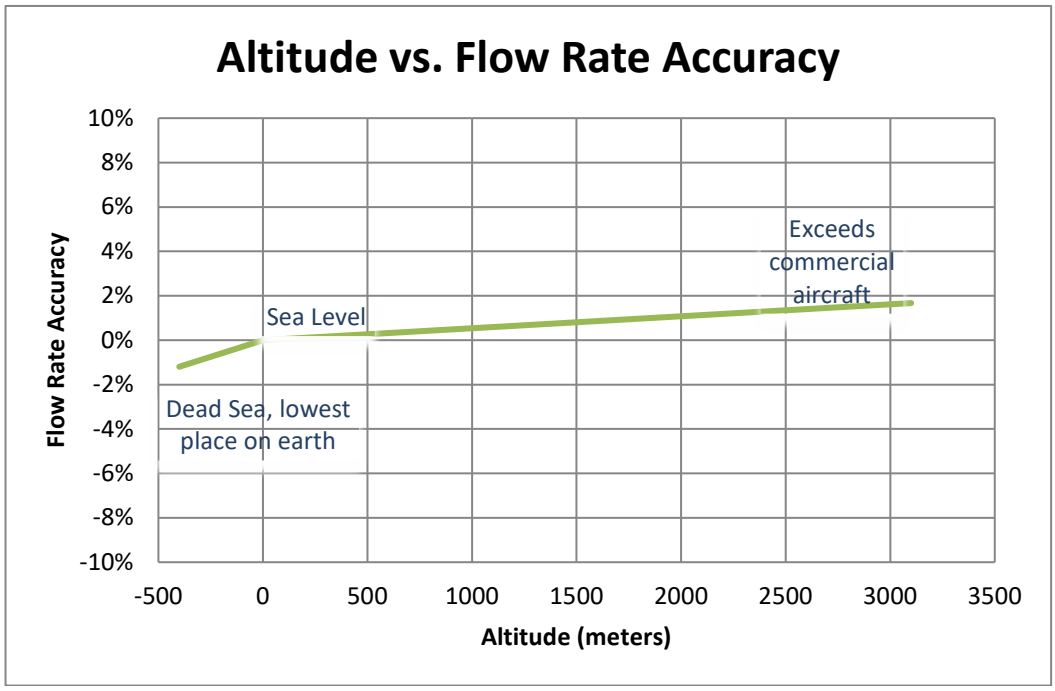
The Prometra II Pump was designed such that changes in pressure or temperature in normal operating environments do not affect the pump's operation.

Measurement error

The apparent flow rate based on clinical measurements can vary due to measurement error (e.g. syringe measurement accuracy, human error, and the volume of fluid in the extension tubing and filter).

Geographical Elevation

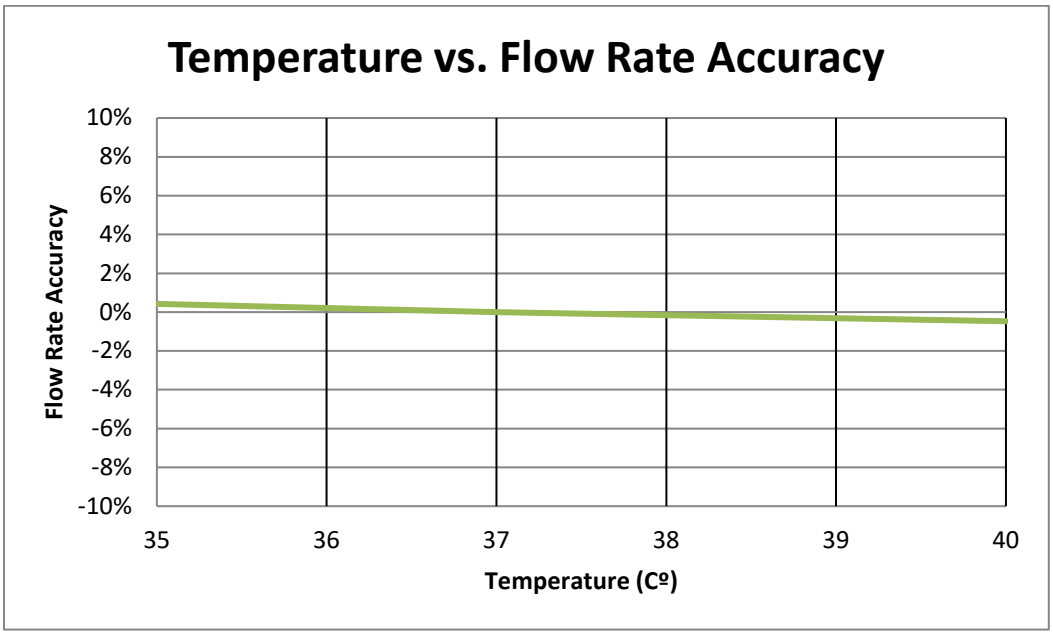
Activities that involve temperature or elevation changes such as skiing, flying, hot-tubbing, or saunas will not affect the operation of the pump.



Activities that involve an increase in environmental pressure of approximately 1 atmosphere or greater, such as scuba diving or hyperbaric therapy may cause the pump to temporarily stop delivering drug. When normal atmospheric pressure is returned, the pump will resume its programmed delivery rate.

Temperature Variation

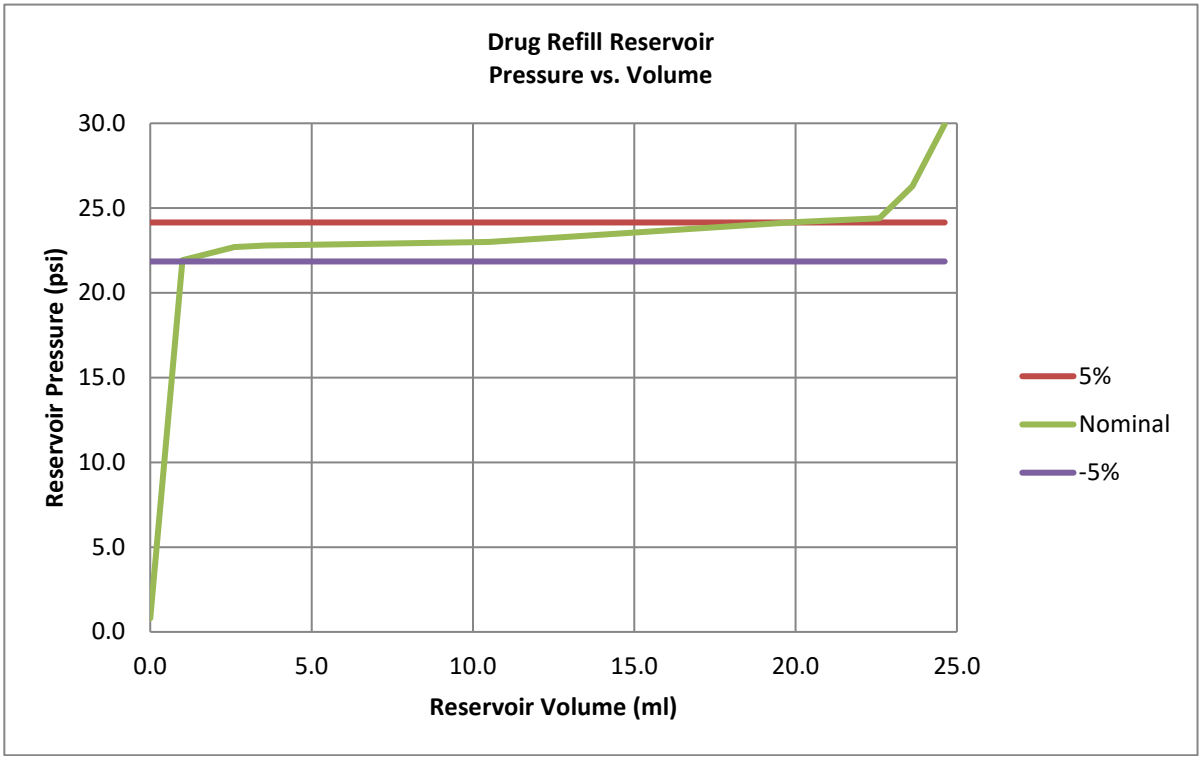
Activities that involve temperature or elevation changes such as skiing, flying, hot-tubbing, or saunas will not affect the operation of the pump. Temperature related therapies such as deep heat therapy, e.g. diathermy, will not affect the operation of the pump.



Flow Rate Accuracy

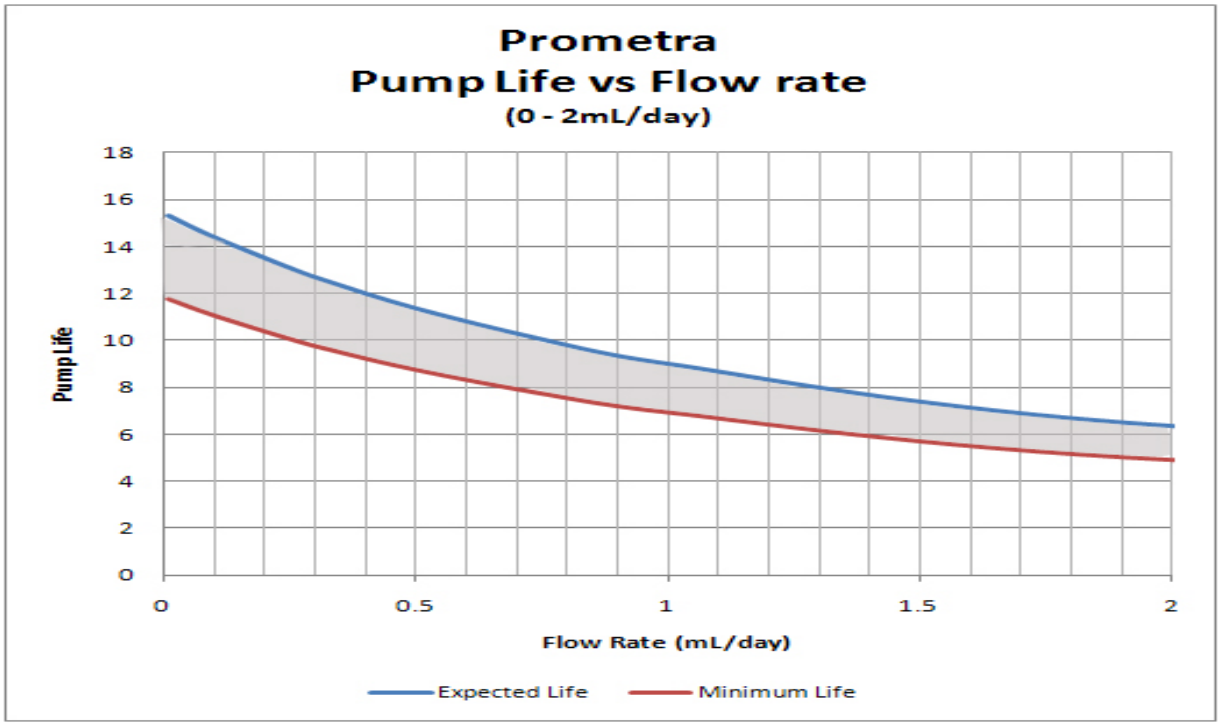
Pump flow rate accuracy was evaluated at multiple infusion rates (≈0.05mL/day – 28.8mL/day), at 37°C body temperature, utilizing both constant flow and variable flow regimes.

Although it is strongly recommended to program the low reservoir volume alarm to 2 mL, it is important to know that reservoir volume down to 1 mL will not affect the operation of the pump. This margin of safety was designed to offer your patients an additional measure of comfort and safety.



Device Longevity

The useful life of the Prometra II Programmable Pump is dependent on the drug delivery rate. The Prometra II Pump utilizes an accumulator and dual-gated valve system to regulate the flow rate in order to conserve energy required for pump operation. The life of the pump is a minimum of 10 years at a drug delivery rate of 0.25mL/day.



Drug Stability

Drug stability has been established for the drug and concentration listed in the table below:

Table: Stability for Drugs Approved for Use

Drug	Manufacturer	Concentration	Duration of Study
Infumorph Preservative-free Morphine Sulfate Sterile Solution	Baxter Healthcare (Infumorph has been acquired by West-Ward Pharmaceuticals)	25 mg/mL, 10 mg/mL	90 days
Baclofen injection (intrathecal)	FDA Approved manufacturers of baclofen injection (intrathecal)	0.5 mg/mL, 2 mg/mL	60 day refill intervals, 180 days total

Issue Date: TBD

An issued or revision date for these instructions is included for the user's information. In the event two years have elapsed between this date and product use, the user should contact Flowonix Medical, Inc. to see if additional product information is available.

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US and Foreign patents issued and pending. Please consult www.flowonix.com for the most up-to-date information.

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