PROMETRA® II PROGRAMMABLE INFUSION SYSTEM DRUG SUMMARY STATEMENT:

Product technical manuals and the appropriate drug labeling must be reviewed prior to use for detailed disclosure.

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 is indicated for use in adult 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.

Contraindications:

Implantation of the Prometra II Programmable Pump 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 drug therapy must be observed and followed per the approved drug labeling.

Warnings:

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:

- 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.

- 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.

Potential Adverse Events:

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.

INFUMORPH INJECTION (INTRATHECAL)

Important Safety Information

Indications and Usage

INFUMORPH is an opioid agonist, for use in continuous microinfusion devices and indicated only for intrathecal or epidural infusion in the management of intractable chronic pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

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.

Use in Specific Populations

Pregnancy: May cause fetal harm
Hepatic and Renal Impairment: May affect the metabolism and excretion of INFUMORPH

Management Of Drug-Related Adverse Events Including Overdose Diagnosis And Treatment

Acute overdose with INFUMORPH can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques. The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to morphine overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. As the duration of effect of naloxone is considerably shorter than that of epidural or intrathecal morphine, repeated administration may be necessary. Patients should be closely observed for evidence of renarcotization. Because the duration of opioid reversal is expected to be less than the duration of action of morphine in INFUMORPH, particularly with epidural or intrathecal morphine, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information. In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

Emergency Technical Support

In the United States, emergency technical support is available for clinicians managing patients with Infusyn Prometra Programmable Infusion Systems: 855-356-9665.

Dosing Considerations

Administration should be limited to use by those familiar with the management of respiratory depression.

- Should be administered by or under the direction of a physician experienced in the techniques of epidural or intrathecal administration.
- Patients should be observed in a fully equipped and staffed environment for at least 24 hours after each test dose and, as indicated, for the first several days after surgery.
- Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse

Initial Dosage: Must be individualized, based upon in-hospital evaluation of the response to serial single-dose epidural bolus injections of regular DURAMORPH (morphine sulfate injection, USP) 0.5 mg/mL or 1 mg/mL, with close observation for analgesic efficacy and adverse effects prior to surgery involving the continuous microinfusion device.

Dosage for Intrathecal Administration: Initial dose range of 0.2 to 1 mg/day for patients with no tolerance to opioids. The range of doses for patients with some degree of opioid tolerance varies from 1 to 10 mg/day. Doses above 20 mg/day should be employed with caution.

- Do not stop INFUMORPH abruptly in a physically dependent patient.

BACLOFEN INJECTION (INTRATHECAL)

Important Safety Information

Indications and Usage

Baclofen injection (intrathecal) is a muscle relaxant and antispastic that is indicated for use in the management of severe spasticity of cerebral or spinal origin. It is intended for use by the intrathecal route in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, only in implantable pumps approved by the FDA specifically for the administration of baclofen injection (intrathecal) into the intrathecal space. Baclofen injection (intrathecal) via an implantable pump should be reserved for patients unresponsive to oral baclofen therapy or those who experience intolerable CNS side effects at effective doses. Patients with spasticity due to traumatic brain injury should wait at least one year after the injury before consideration of long term intrathecal baclofen therapy. Prior to implantation of a device for chronic intrathecal infusion of baclofen injection (intrathecal), patients must show a response to Baclofen Intrathecal in a screening trial. **Please review the dosing and administration section of the baclofen injection (intrathecal) prescribing information for further details**.

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 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 intrathecal baclofen. 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 intrathecal, increase the risk of surgical complications and complicate dosing.
- Reservoir refilling must be performed by fully trained and qualified personnel following the instructions for use provided in the Refill Kit IFU.
- Following pump implantation, and for each adjustment of the dosing rate of the pump and/or concentration of baclofen intrathecal, the patient should be monitored closely.
- In the event of a likely overdose, the patient should be taken immediately to a hospital for evaluation.
- Concomitant oral antispasticity medication should be discontinued to avoid possible overdose or adverse drug interactions.
- The dose of Baclofen injection (intrathecal) should be reduced slowly if the drug is discontinued for any reason, except in an emergency situation.

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.

Use in Specific Populations

There are no adequate and well controlled studies in pregnant women or nursing mothers. Baclofen Intrathecal use during pregnancy should be left to the discretion of the physician and only if the potential benefit outweigh the risks.

Safety and effectiveness of the Prometra Infusion System in pediatric patients with baclofen below the age of 12 has not been investigated or established.

Use with caution in patients with impaired renal function (dose reduction may be necessary), patients with a history of autonomic dysreflexia, patients suffering from psychotic disorders, schizophrenia, or confusional states.

For more information, including BOX WARNING, refer to baclofen injection (intrathecal) prescribing information.

MANAGEMENT OF DRUG-RELATED ADVERSE EVENTS INCLUDING OVERDOSE AND WITHDRAWAL

Clinicians should use caution and monitor for any adverse events during all phases of intrathecal baclofen therapy. Please refer to the baclofen injection (intrathecal) prescribing information for a complete listing of drug-related adverse events.

Patients' sensitivity to baclofen injection (intrathecal) may vary. Most common side effects are: hypotonia, somnolence, nausea/vomiting, headache, dizziness, convulsion, and urinary retention.

Refer to the Prometra Indications, Drug Stability, and Emergency Procedures manual (PL-39701) for specific management instructions.

OVERDOSE OF BACLOFEN INJECTION (INTRATHECAL)

Always be alert to the symptoms of overdose. Early symptoms of overdose include: drowsiness, lightheadedness, dizziness, somnolence, respiratory depression and hypothermia.

Overdose can potentially progress to seizures, rostral hypotonia, loss of consciousness and potential coma.

To limit the risk of a potential overdose:

- Ensure that the staff is properly trained on refill and programming procedures as well as symptoms of overdose prevention and management.
- Patient and family should be educated regarding the signs and symptoms of overdose.

- 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.
- Perform the screening test, dose adjustments, and any pump or catheter access in a medically-supervised and adequately-equipped environment.
- Ensure accurate programming of the pump.

EMERGENCY TECHNICAL SUPPORT

An emergency procedure and treatment protocol for overdose is available. Emergency technical support is available 24 hours/day for clinicians managing patients with Prometra Programmable Infusion Systems: 855-356-9665.

WITHDRAWAL OF BACLOFEN INJECTION (INTRATHECAL)

Always be alert to the symptoms of baclofen injection (intrathecal) withdrawal. Baclofen withdrawal should be treated as a medical emergency.

Early symptoms of withdrawal include: return to baseline spasticity, pruritus, hypotension, paresthesias, and priapism.

Symptoms of advanced withdrawal include: high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity.

If left untreated, withdrawal may lead to rhabdomyolysis, multiple organ-system failure, and/or death.

Baclofen injection (intrathecal) withdrawal may mimic the following conditions: autonomic dysreflexia, sepsis, malignant hyperthermia, neuroleptic-malignant syndrome, and other conditions associated with a hypermetabolic state.

SAFEGUARDS AGAINST WITHDRAWAL

All patients receiving baclofen injection (intrathecal) are potentially at risk. Abrupt discontinuation of baclofen is the primary cause of withdrawal. To safeguard against withdrawal:

- Education of staff, patient, and family members on the signs, symptoms and prevention of withdrawal are important.
- Instruct staff on emergency procedures and treatment of withdrawal.
- Ensure accurate programming of the pump.

DIAGNOSIS AND TREATMENT

To prevent potentially life-threatening effects, rapid diagnosis and treatment of baclofen injection (intrathecal) withdrawal in an emergency department or intensive-care setting are important.

The suggested treatment is restoration of intrathecal delivery at the same dose. However, if treatment is delayed, GABA-ergic agonistic drugs such as oral or enteral baclofen, or oral, enteral,

or intravenous benzodiazepines may prevent potentially fatal consequences. Do not rely on oral or enteral baclofen alone to prevent withdrawal progression.

EMERGENCY TECHNICAL SUPPORT

In the United States, emergency technical support is available for clinicians managing patients with Infusyn Prometra Programmable Infusion Systems: 855-356-9665.

DOSING CONSIDERATIONS

Clinicians must weigh the benefits of increased dose titration to achieve optimal spasticity control with the risks of adverse effects. Patients should be observed closely for symptoms of drug overdose, withdrawal, tolerance, and ineffective dosing during titration.

Prometra Programmable Infusion Systems provide precise dose titration and flexible programming options. The lowest dose with an optimal response should be used. During each dosing rate adjustment, close patient monitoring is required.

Drug dosage will vary with each patient. Encourage patients to notify their clinicians of unusual symptoms, drug overdose, withdrawal, or loss of drug effect.

In accordance with drug labeling for pediatric patients, the starting screening dose for pediatric patients is the same as in adult patients, i.e., 50 mcg. However, for very small patients, a screening dose of 25 mcg may be tried first. Patients who do not respond to a 100 mcg intrathecal bolus should not be considered candidates for an implanted pump for chronic infusion.

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