

Hazard Alert
SynchroMed® II and SynchroMed® EL Implantable Infusion Pump –
Priming Bolus
TGA Reference: RC-2013-RN-00677-1

This letter provides important safety information and patient management recommendations regarding the unintended delivery of drug during the priming bolus function for the SynchroMed® implantable infusion pump. This unintended delivery of drug can contribute to patient overdose or underdose symptoms which may be clinically relevant. Please see the attached **Potential Impact of Drug Mixing during Priming Bolus** for more information.

Background and nature of the issue:

The SynchroMed priming bolus function is intended to quickly advance drug from the pump reservoir to the catheter tip to allow for therapy initiation while the patient remains under medical supervision. Although drug is not intended to be delivered to the cerebrospinal fluid (CSF) during the priming bolus, mixing of the drug and non-drug (sterile water/CSF) fluids occurs at the high infusion rates used during a priming bolus. Mixing results in the unintended delivery of drug prior to the end of the programmed bolus, as well as dilution of some of the drug remaining in the catheter at the end of the bolus. Patients will receive unintended drug at a high rate of infusion in the CSF during the priming bolus, and a period of reduced concentration of drug will occur following the priming bolus.

Medtronic has performed preliminary bench testing of pumps and catheters to characterize the extent of drug mixing during a priming bolus. It is clear that the amount of drug delivered during the priming bolus procedure is related to the concentration of the drug; however clinical relevance is not fully understood. As part of the evaluation of the priming bolus, Medtronic also reviewed previously reported adverse events of overdose, underdose, and death following an infusion system implant or revision. Since drug mixing will occur any time the priming bolus is used with a SynchroMed pump, it is reasonable to expect that the resulting unintended drug delivery is a contributing factor to adverse events involving overdose and underdose. These adverse events will vary depending on the drug being infused, but could include lack of therapeutic effectiveness, confusion or altered mental state, sleepiness, nausea, respiratory depression, coma or death. Medtronic has been unable to establish a definitive causal relationship to priming bolus due to a number of other potential contributing factors including: drug dosage, the patient's medical history, and the concomitant use of other drugs, such as oral opioids and other central nervous system (CNS) depressants.

Recommendations for Patient Management and Monitoring after Initiation of Intrathecal Therapy:

Medtronic recommends following published guidance for managing all patients with intrathecal therapy, in addition to the following:

- Continue use of the priming bolus procedure to ensure that therapy is initiated while the patient is under medical supervision.
- Monitor all patients following start or restart of intrathecal therapy, as recommended below. The post-procedure monitoring period will depend upon specific drug, dose administered and patient co-morbidities.
 - Opioids - For patients initiated or reinitiated with intrathecal infusion of opioids, monitoring with pulse oximetry for a minimum of 24 hours or until they demonstrate stable neurological, respiratory and cardiac function in a facility equipped with emergency airway management, oxygen, naloxone for treatment of opioid overdose and other emergency services is recommended. Please refer to additional instructions provided in the drug product labeling (including Infumorph^{®1}) and published guidance.²

¹Infumorph [package insert]. West-Ward Pharmaceuticals, Eatontown, NJ; September 2011. <http://www.west-ward.com/images/files/package/Infumorph%20200&500%20PI.pdf>. Accessed April 17, 2013.

- Baclofen – Patients initiating or reinitiating an intrathecal infusion of baclofen should be monitored in a facility that provides experienced nursing observation, with the ability and personnel for emergency airway management and ventilator support readily available. Patients should be monitored for a minimum of 8 hours or until they demonstrate stable neurological, respiratory and cardiac function.
- Consider priming the pump prior to implant in the patient and before connection to the catheter (back table prime) to decrease the risk of overdose, especially in patients receiving higher concentration opioid drug solutions and low total daily dose.
- Educate caregivers and family members to recognize the signs and symptoms associated with intrathecal drug therapy complications.²
- Patients who are receiving intrathecal baclofen and who receive a catheter-only priming bolus with or without a CAP aspiration will take longer to reach full intended drug concentration. Dose titration may need to be supplemented with oral baclofen to treat spasticity until the optimal intrathecal dose is obtained.
- Physicians should advise patients to avoid using concomitant drugs that may cause respiratory or CNS depression while intrathecal therapy is being initiated or resumed.

Additional Resources:

We are committed to continuing to advance the practice of intrathecal drug delivery and to enable you to manage your patients in a safe and effective manner. If you have questions, please contact your Medtronic field representative. This important patient management information is also available on Medtronic's healthcare professional website under the heading "Advisories".

Please return any explanted SynchroMed II pump to Medtronic Returned Products Analysis. Contact your Medtronic Neuromodulation representative. Please report any malfunction or adverse event related to a device to your Medtronic Neuromodulation representative.

²Deer, T. R., Prager, J., Levy, R., et. al. (2012), Polyanalgesic Consensus Conference—2012: Recommendations on Trialing for Intrathecal (Intraspinal) Drug Delivery: Report of an Interdisciplinary Expert Panel. *Neuromodulation: Technology at the Neural Interface*, 15: 467–482.

Appendix 1: Potential Impact of Drug Mixing During Priming Bolus

Medtronic convened a panel of experts to review the initial data, and the following patient populations were identified as having increased risk:

- Opioid-naïve or opioid-sensitive patients undergoing new pump and catheter implants, especially those prescribed high concentration drug solutions at the lowest daily doses, are at increased risk of intrathecal drug overdose.
- Patients who are highly sensitive to baclofen and require low daily doses may experience effects of increased drug immediately following the priming bolus.
- For baclofen patients undergoing pump or catheter revision with or without a catheter access port (CAP) aspiration, a delay in achieving the intended therapeutic dose will occur and may result in temporary return of symptoms such as increased spasticity.

Note: Other clinically relevant patient populations may exist in addition to these examples.

The amount of drug delivered to a patient during a priming bolus is impacted by multiple factors, including the type of priming bolus (full system or catheter only prime), specific drug concentration, catheter length and diameter, priming volume, priming duration and patient characteristics. High concentration drugs combined with flow rates associated with priming bolus will increase the extent of mixing and the amount of drug delivered prior to the end of the priming bolus. For patients requiring a low daily dose, the amount of drug introduced during the priming bolus will represent a larger proportion of the intended daily dose with the potential for greater clinical effect. In addition, it may take longer for patients to receive the full intended dose if a catheter only prime is performed with or without a catheter access port (CAP) aspiration.

The following full system prime scenarios, while preliminary, indicate current understanding:

- A full prime of the pump and catheter (using current recommended protocol) with a post-prime flow rate at the lowest settings may result in a delivered dose in the range of ~100% of the intended daily dose during the priming bolus. While a priming bolus takes 20-30 minutes to complete, diluted drug may exit the distal tip of the catheter during the final three to seven minutes of the priming bolus. For patients using morphine at a concentration of 30 mg/ml receiving the lowest possible dose of morphine (1.4 mg/day using 0.048 ml/day flow rate) this may represent a bolus delivery in the range of 1.4 mg (~100% of the daily dose). For patients using morphine at a concentration of 10 mg/ml receiving the lowest possible dose of morphine with this concentration (0.5 mg /day using 0.048 ml/day flow rate) this may represent a bolus dose in the range of 0.5 mg.
- For patients receiving a more clinically common dosing regimen of 10 mg/ml and a therapeutic goal of 3 mg /day (using 0.300 ml/day flow rate) the patient may receive a bolus in the range of 0.75 mg (~25% of the intended daily dose) during the priming procedure.
- In the situation where the pump is fully primed prior to attachment of the catheter followed by a catheter only priming bolus (consistent with current recommended protocol) even with the highest concentration tested (25 mg/ml) the amount of drug delivered during the priming bolus is believed to be negligible.

The following scenarios, while preliminary, indicate the current understanding of catheter only prime scenarios (with or without CAP aspiration):

- A standard catheter only prime (using the current recommended protocol) with a post-prime flow rate of 0.048 ml/day may result in a 9 hour delay until drug delivery.
- For patients receiving a more clinically common dosing regimen using 0.300 ml/day, may result in up to a 3 hour delay until drug delivery.
- After 24 hours the intended daily dose is achieved in both of the above scenarios.