

Urgent Field Safety Notice

SynchroMed® II Implantable Drug Infusion Pump

Overinfusion

Medtronic reference: FA596

Dear Healthcare Professional,

This letter provides important new information regarding overinfusion associated with the SynchroMed® II Implantable Pump. Overinfusion can result in a life-threatening overdose and can also result in drug withdrawal due to premature emptying of the pump. Due to the low reported rate of occurrence of this issue and the inability to predict which pumps may be at risk, Medtronic is not recommending prophylactic replacement of pumps.

This communication is based on information available to date and was developed in collaboration with clinical experts. Medtronic continues to investigate this issue and we are committed to providing updates as more information becomes available.

Explanation of the Issue:

Medtronic detected an upward shift in reports of occurrence for overinfusion. Overinfusion is defined as an infusion rate exceeding the programmed infusion rate by more than 14.5% as described in the labeling (see enclosed *flow rate accuracy* section from the SynchroMed II Implant Manual). When overinfusion occurs, it will result in a volume discrepancy at pump refill, where the volume withdrawn from the pump is less than the volume expected. The cause(s) for pump malfunction leading to overinfusion remains under investigation and has not been linked to any specific pump lot, drug used, or geographical area. Based on reports, the onset of overinfusion has occurred as early as five months after implant and throughout the service life of the pump. Reports received indicate that once a pump has started to overinfuse, infusion rates can continue to increase, in some cases abruptly.

Scope and Severity:

Based on current data from Medtronic's prospective, long-term multi-center registry study (ISPR), the occurrence rate for overinfusion is less than 0.16%¹.

As of November 18, 2013, 76 pumps have been confirmed for overinfusion through returned product analysis since the introduction of the device in 2003:

- 44 were explanted for reasons consistent with overinfusion.
 - 14 reports of life-threatening overdose
 - 27 reports of non-life threatening overdose and/or withdrawal
 - 3 reports of volume discrepancy without overinfusion symptoms
- 32 were explanted for reasons other than overinfusion. However, routine testing of returned pumps found these pumps to be overinfusing.

Adverse events associated with overinfusion will vary depending on the drug being infused, but may include confusion or altered mental state, sleepiness, nausea, respiratory depression and coma, with the risk of death. Overinfusion may lead to emptying of the pump prior to a planned refill and therefore may present clinically as an interruption of therapy including lack of therapeutic effect and withdrawal syndrome. There has not been a report of a patient death associated with this issue.

The low reservoir alarm in the SynchroMed II is designed to activate based on programmed flow rates and starting volumes. The device does not measure actual reservoir volume and in the context of overinfusion the reservoir may empty entirely without activating an alarm. It is not possible to detect the issue other than by following the recommendations below.

Recommendations (Developed in collaboration with clinical experts):

- Medtronic **does not** recommend prophylactic removal of SynchroMed II pumps.
- Educate patients, caregivers and family members to recognize the signs and symptoms associated with intrathecal drug therapy overdose, underdose or withdrawal.
- At every refill visit, question and examine the patient for signs and symptoms of overdose, underdose or withdrawal.
- Follow the labeled refill instructions, so that any volume discrepancy can be detected based on the amount of medication withdrawn prior to refill (see guidelines below).
- At every refill visit record the actual and expected reservoir volume.
- Review prior refill data to identify any changes in volume discrepancy over time. If there are increases in volume discrepancy over time (volume withdrawn from the pump is less than expected) or if there is a volume discrepancy of more than 2 ml:
 - Evaluate for other causes, such as unrecognized partial pocket fill, self-aspiration of reservoir medication, and less than full reservoir at prior refill.
 - If overinfusion is strongly suspected clinically monitor the patient and consider pump replacement. The decision to replace the pump should take the following factors into consideration: history of pump volumes, magnitude of the volume discrepancy, presence/severity of overdose symptoms, and the individual patient situation.
 - To stop delivery of drug from a pump suspected of overinfusion, program a “therapy stop”, which sets the pump to minimum rate, and remove any remaining drug from the reservoir to avoid continued drug delivery.
 - Reducing the dose and/or concentration will not correct overinfusion because infusion rates may increase over time.

Important Guidelines: Always follow pump refill instructions per the device labeling. The following steps should be conducted during each pump refill procedure to allow detection of an overinfusing pump:

- Aspirate all fluid from the reservoir until air bubbles no longer appear in the syringe, and record as the amount withdrawn.
- Compare the amount withdrawn from the pump reservoir with the expected volume displayed by the pump programmer. The amount withdrawn should approximately equal the expected volume.
- Determine fill volume (fill with no more than the labeled reservoir volume, 20 or 40 ml).
- Accurately measure the volume to be instilled.
- If you are unsure whether drug was injected correctly into the pump, completely aspirate the pump to verify that the entire injected volume of drug has been removed.
- Ensure that refill dates are chosen sufficiently in advance of the low reservoir alarm date so the pump does not run dry.

In case overinfusion is strongly suspected please contact Medtronic Neuromodulation Technical Services at <xxxxx>.

Medtronic has notified the Competent Authority of your country of this action. Please share this notification with others in your organization as appropriate.

We are committed to continuing to improve our product performance and services to enable you to manage your patients in a safe and effective manner. If you have questions, please contact your Medtronic sales representative.

Sincerely,

Enclosed: Flow rate accuracy as described in the SynchroMed II Implant Manual.

ⁱ There have been four reports of overinfusion in 5,765 SynchroMed II pumps included in Medtronic's prospective, long-term multi-center registry study (ISPR), providing a 95% confidence that the occurrence rate is less than 0.0016 (0.16%).

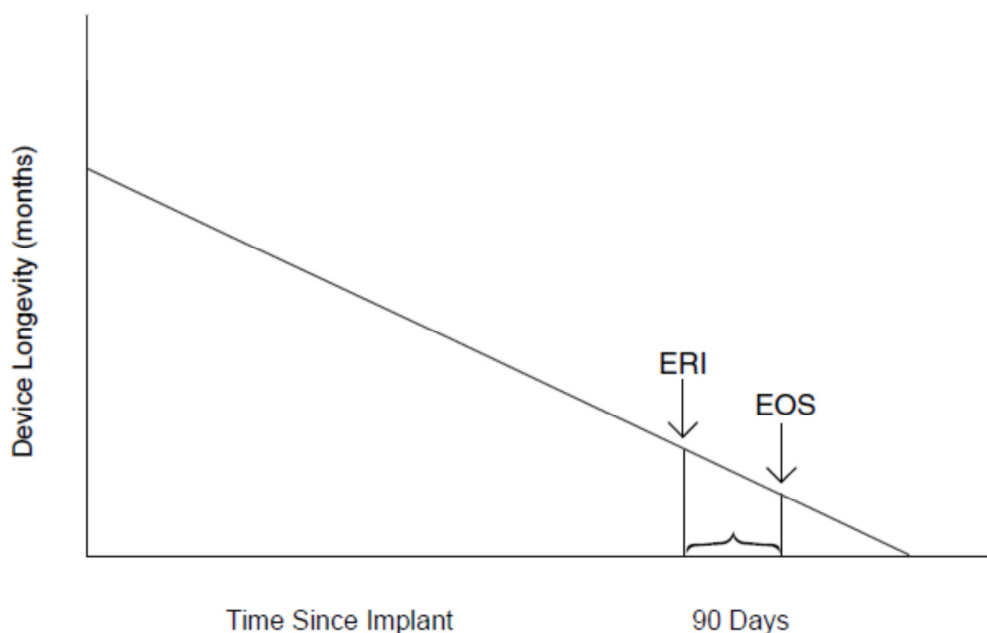


Figure 4. ERI and EOS.

Flow rate accuracy

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

Measurement error

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

Fluid volume

The flow rate of the pump varies slightly with the volume of fluid in the pump reservoir. The pump flow rate decreases as the reservoir volume approaches 1 mL. The pump flow rate decreases rapidly and then stops as the reservoir volume decreases from 1 mL to 0 mL. Therefore, the pump should be refilled prior to reaching 1 mL or less. Typically, the flow rate

decreases by about 4% as the volume is reduced from the half-full volume to a volume of 1 mL. The usable volume is the reservoir volume minus 1 mL (Figure 5).

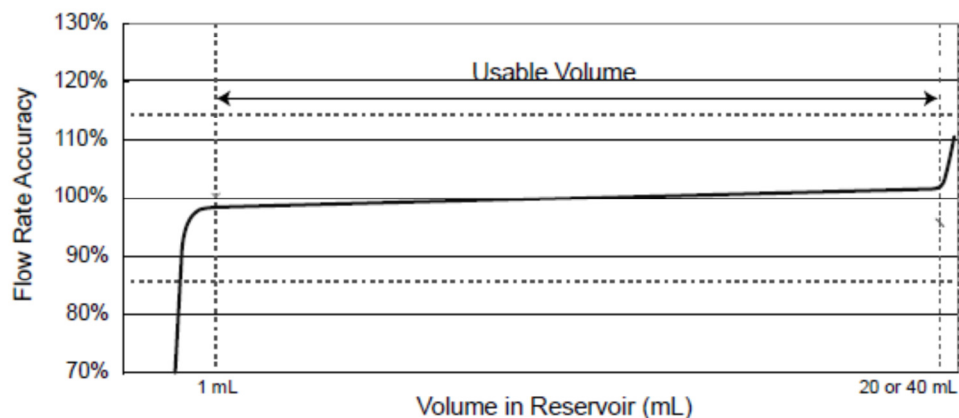


Figure 5. Flow rate accuracy as a function of fluid volume in reservoir.

Environmental conditions

Body temperature

The flow rate of the pump varies with body temperature. The flow rate increases as the temperature increases above 37 °C and decreases as the temperature decreases below 37 °C (Figure 6).

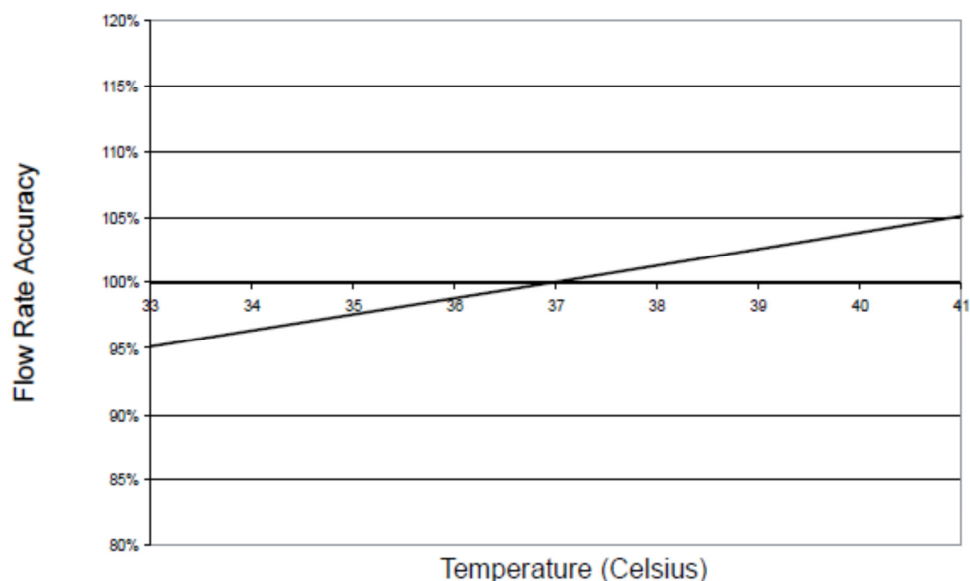


Figure 6. Flow rate accuracy as a function of temperature (typical effect).

Atmospheric pressure

Patients living or traveling (eg, airline flights, mountain climbing) at altitudes above sea level are exposed to lower atmospheric pressures. Within days of exposure to the lower pressures, the flow rate of the pump can increase and then stabilize at the higher flow rate. In circumstances where a potential increase in flow rate may pose a risk to a patient, reprogramming the infusion prescription offsets this higher flow rate (Figure 7).

In rare instances, exposure to the lower atmospheric pressure can cause the pump to deliver more than 14.5% of the programmed flow rate while the patient is exposed to the lower pressure. Consider changes in drug concentrations or changes to pump programming for patients exposed to lower pressures.

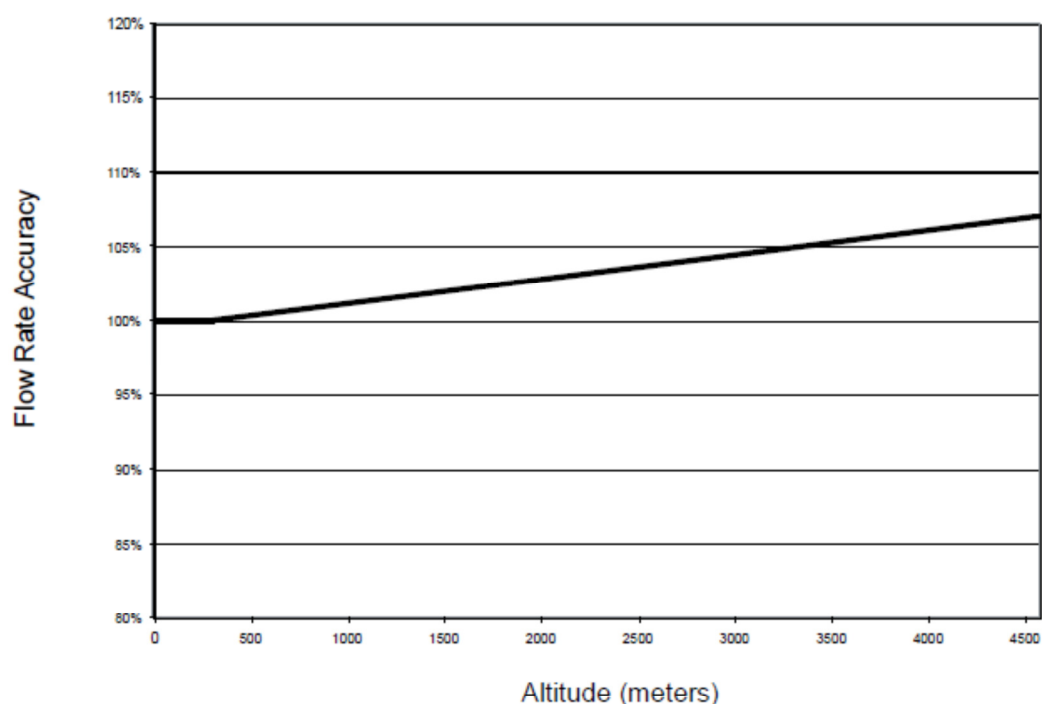


Figure 7. Flow rate accuracy as a function of altitude (typical effect).

Declaration of Conformity

Medtronic declares that this product is in conformity with the essential requirements of Directive 1999/5/EC on Radio and Telecommunications Terminal Equipment and Directive 90/385/EEC on Active Implantable Medical Devices.

For additional information, contact the appropriate Medtronic representative listed on the inside back cover of this manual.