Medtronic

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Dear Healthcare Professional,

SynchroMed® II Implantable Drug Infusion Pump: Update to the April 2014 Communication on Overinfusion

Medtronic International Ltd is issuing this letter to inform you of an update to Medtronic's April 2014 notification regarding the potential for SynchroMed II pump overinfusion. This notification updates information related to contributing causes, occurrence rate and patient management recommendations. Consistent with the previous communication, Medtronic is not retrieving SynchroMed II pumps from the field or recommending prophylactic replacement of the pumps. Please share the enclosed recommendations and this update with personnel responsible for the management of patients implanted with a SynchroMed II pump.

Updated Information on the Issue of Overinfusion

Explanation of the Issue:
"Overinfusion" is defined as the delivery of more drug volume than the programmed rate, exceeding the pump's flow rate accuracy specification. Pump reservoir contents aspirated during a refill procedure that are less than expected may indicate that the pump has overinfused. Overinfusion may or may not be associated with clinically relevant symptoms. When the pump delivers more drug volume than the programmed rate, patients may experience overdose symptoms, and the pump reservoir will deplete more quickly than expected. Patients may experience underdose or withdrawal symptoms if the drug is depleted prior to the scheduled refill date from an overinfusing pump.

The low reservoir alarm of an overinfusing pump will not sound if the pump reservoir is prematurely depleted. The low reservoir alarm is calculated from the pump's programmed delivery rate and is not a direct measurement of the actual drug volume in the pump reservoir. Therefore, it is important to follow the enclosed recommendations.

Investigation Results on Risk Factors:
Medtronic's investigation has not identified any single factor that results in overinfusion; rather the interaction of several variables increases the likelihood that a given pump will overinfuse. Some risk factors are associated with normal variability with pump components and manufacturing processes, while other factors are associated with clinical use conditions. Examples of clinical use conditions that have been shown to increase the likelihood of overinfusion are the use of nonindicated drug formulations, overfilling of the pump reservoir, operation of the pump with no fluid in the reservoir, catheter occlusion, and pump stops or motor stalls lasting more than 48 hours.

Occurrence Rate Based on Registry Data:
Five occurrences of overinfusion have been identified in Medtronic's prospective, long-term multi-center registry study (Product Surveillance Registry) as of January 2016,

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resulting in a rate estimate of less than 0.14%[1] (approximately 1-in-700). All 5 occurrences of overinfusion noted in the Registry were associated with pumps used to infuse drug formulations that were not indicated for use with the SynchroMed II pump.

Reports of Adverse Events:
Since commercial release of the SynchroMed II pump, over 238,000 pumps have been implanted. During Medtronic's investigation of overinfusion, complaint data and returned product analysis were assessed, resulting in 103 pumps with related adverse events through 05 July 2016. Medtronic has been unable to establish a definitive causal relationship between the adverse events and overinfusion due to potential contributing factors. However, it is reasonable to conclude that overinfusion was a contributing factor in these cases. Other factors that may have contributed to an adverse event are: infused 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.

Reported patient outcomes associated with these adverse events ranged from temporary discomfort to life threatening overdose and/or withdrawal as well as two reports of death. While the full drug history of these pumps is unknown, 99 of the 103 pumps were associated with nonindicated drug formulations in use at the time of the pump's last refill. The estimated implant duration for the 103 pumps is 3.7 years (with a range of 0.4 – 6.4 years).

Advisory to Healthcare Professionals

Recommendations (Developed in collaboration with clinical experts):

- Medtronic does not recommend prophylactic removal of SynchroMed II pumps.
- To minimize the risk of overinfusion, use the approved/indicated drug formulations for the SynchroMed II pump. The use of nonindicated drug formulations (such as admixtures, compounded drugs and unapproved drug concentrations) increases the likelihood of overinfusion.
- 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 refill instructions in the approved labeling so that any volume discrepancy can be detected based on the amount of medication withdrawn (expected) prior to refilling with new solution. (See Important 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:

[1] Through 31 January 2016, there have been five reports of overinfusion in 7,505 SynchroMed II pumps included in Medtronic's prospective, long-term multi-center registry study (PSR, formerly ISPR), providing an upper 95% confidence bound on the occurrence rate of 0.0014 (0.14%). Based on investigation results, this rate is not significantly changed from the 0.16% upper 95% confidence bound reported in the April 2014 communication.

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- Evaluate for other potential causes of volume discrepancy, for example: inaccurate volume measurements, incomplete pump aspiration, incorrect volume entry into clinician programmer at refills, unrecognized partial pocket fill, or aspiration of pump medication by patient or caregiver.
- Evaluate for factors that may increase the likelihood of overinfusion. These factors include: nonindicated drug formulations, overfilling of the pump reservoir, operation of the pump with no fluid in the reservoir, catheter occlusion, and pump stops or motor stalls lasting more than 48 hours.
- If overinfusion is suspected, consider scheduling an interim pump reservoir volume check prior to the next scheduled refill. Evaluate and question the patient for symptoms consistent with overinfusion. If after the interim check, overinfusion continues to be of concern, clinically monitor the patient and consider pump replacement.
- Reducing the dose and/or concentration is not a recommended mitigation for overinfusion due to the identified failure modalities.
- To stop delivery of drug from a pump suspected of overinfusion, program a "therapy stop," which sets the pump to minimum rate, and aspirate any remaining drug from the reservoir to avoid continued drug delivery.

Healthcare professionals are advised to do the following:
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 the refill date is chosen sufficiently in advance of the low reservoir alarm date so the drug reservoir of an overinfusing pump is not prematurely depleted.

Reporting of Adverse Event

Inform Medtronic Neuromodulation Technical Services if overinfusion is suspected. Please return any explanted products to Medtronic for mechanical and functional analysis. To minimize changes in the pump condition after explant, pumps that are suspected of overinfusion should be returned with fluid in the reservoir, set to a minimum infusion rate, and returned using the designated returned product mailer. Your local Medtronic representative can assist you in return of product.

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Healthcare professionals are advised to report any adverse events and/or suspected adverse reactions associated with these devices to your local Clinical Representative Mr. Jason Ee at +65 9835 7526, Email: jason.ee@medtronic.com, Fax: +65-6776 6355.

[redacted]

Yours Sincerely,
Shirley Loh
Marketing Director

Enclosure: *Physician / HCP Reply Form*