Urgent Field Safety Notice

Use of Unapproved Drugs with the SynchroMed® Implantable Infusion Pump

IMPORTANT MEDICAL DEVICE INFORMATION

Medtronic ref : FA553

November 2012

Dear Doctor,

This letter provides important updated information on Medtronic Neuromodulation's continuing efforts to investigate and communicate the impact of unapproved drugs on the performance of the SynchroMed infusion pump system. Use of unapproved drugs with SynchroMed pumps can result in an increased risk of permanent motor stall and cessation of drug infusion. Approved drugs for infusion therapy with the SynchroMed systems contain morphine sulfate, morphine hydrochloride, floxuridine, methotrexate, baclofen or ziconotide in solution. More drug detail is attached to this letter in the *Summary of Approved Drugs*.

Explanation of the Issue:
Based on data from Medtronic's Implantable Systems Performance Registry (ISPR), the *overall* failure rate of the SynchroMed II pump at 78 months post implant is 2.4% when used to dispense approved drugs, and 7.0% when used to dispense unapproved drugs. The use of unapproved drugs can lead to intermittent or permanent pump motor stalls which may be reported as a loss of or change in therapy. Therapy changes could potentially result in serious injury and/or death. Pumps can experience motor stalls when used with either approved or unapproved drugs, however pump motor stalls have been reported at a significantly lower rate when approved drugs are exclusively used.

Medtronic continues to investigate motor gear corrosion, which has been identified as a primary contributor to permanent motor stall in both SynchroMed II and SynchroMed EL pumps. Enclosed you will find a document titled *Increased Risk of Motor Stall and Loss of or Change in Therapy with Unapproved Drug Formulations* that provides additional details.

Recommendations:
To minimize the potential for motor stall, only use the approved drugs that are identified in the SynchroMed infusion system labeling. Do not use compounded drugs, unapproved concentrations or unapproved formulations.

- Continue to monitor patients closely for the possible return of baseline symptoms. A return of baseline symptoms could potentially indicate pump damage.
- Reinforce with patients and caregivers information on the signs and symptoms of withdrawal due to therapy cessation, and the importance of contacting their healthcare provider immediately if these signs and symptoms appear.

- The SynchroMed II pump is designed with a critical alarm for pump motor stall. For patients implanted with a SynchroMed II pump, you can change the critical alarm interval frequency to sound every 10 minutes.
    - Remind patients, their caregivers, and your appropriate staff members to be alert for pump alarms.
    - At implant or follow-up visits, perform an alarm test to provide an opportunity for patients and caregivers to hear and differentiate between the critical and non-critical pump alarms.
    - For patients with a Personal Therapy Manager (PTM), the PTM will show alarm code 8476 if there is an active alarm.
- Retrieve logs when interrogating the SynchroMed II pump in order to check for motor stall events. Note that a temporary motor stall with recovery is expected behavior when the pump is exposed to a strong magnetic field such as during an MRI. Medtronic Technical Services can be contacted for further assistance evaluating motor stall events on logs.

Transmission of this Field Safety Notice:
This notice needs to be passed on to all hospital pharmacists who prepare drug refills, to all health care professionals who perform pump refills and in general to those who need to be aware within your organisation or to any organisation where the potentially affected devices have been transferred.

Please transfer this notice to other organisations on which this action has an impact.

Please maintain awareness on this notice and resulting action for an appropriate period to ensure effectiveness of the corrective action.

Additional Information:
We are committed to continuing to advance the practice of intrathecal drug delivery and to improve our product performance and services to enable you to manage your patients in a safe and effective manner. You can access product performance information online at: http://professional.medtronic.com.

The Competent Authority of your country has been informed of this action.

We regret any difficulties this may cause you and your patients. If you have any questions, or if we can be of assistance, please contact your local Medtronic Representative or Medtronic Technical Services at <xxxxx>

Sincerely,

Country BU Manager

Enclosures:
- Increased Risk of Motor Stall and Loss of or Change in Therapy with Unapproved Drug Formulations
- Summary of Approved Drugs

Increased Risk of Motor Stall and Loss of or Change in Therapy with Unapproved Drug Formulations

Summary

Medtronic Neuromodulation has confirmed through engineering analyses that the use of unapproved drug formulations can increase the risk of pump motor stall due to corrosion in the SynchroMed infusion systems. Use of unapproved drugs or fluids can result in increased risks to the patient and permanent damage to the pump. This can lead to permanent pump stalls requiring surgical replacement and a loss or change in therapy, which may lead to a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug underdose. Unapproved drug formulations include drugs not listed in the labeling including admixtures, compounded drugs, and unapproved drug concentrations. Labeling is provided with the pump and catheter systems. Additional copies of approved product labeling can be obtained from your Medtronic representative.

How Does Corrosion Damage Occur?

Corrosive agents (e.g. chloride ion, sulfate ion) originating from drug formulations can permeate through the internal pump tubing and initiate corrosion of internal components. Some factors that can increase the permeation rate of the corrosive agents in the drug formulation include hydrophobicity, degree of positive ionization, impurities, preservatives, pH adjustments, and concentrations adjustments. Permeation of corrosive agents originating from many unapproved drug formulations can occur at significantly higher rates than for approved drug formulations.

In addition to permeation, damage can occur as a result of a leak in the pump tube resulting in direct exposure of internal pump components to corrosive agents from the drug solution. The manufacturing process includes inspection of pump tubes to guard against leaks at the time of manufacturing.

Clinical Significance

Intermittent or permanent pump motor stalls may be reported as a loss or change in therapy, which may lead to a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug underdose.

Confirmed Unapproved Drugs That Have Resulted in Permanent Pump Stalls

Through returned product analysis and in vitro testing, Medtronic Neuromodulation has confirmed that unapproved drugs and drug formulations that have caused pump damage resulting in pump motor stalls include, but are not limited to, the following:

- Compounded drugs, including some formulations of baclofen and morphine
- Admixtures for severe spasticity therapy containing baclofen with clonidine, and baclofen mixed with other drugs
- Admixtures for chronic pain therapy containing fentanyl and/or sufentanil, bupivacaine, clonidine, hydromorphone, morphine, and baclofen.

Other unapproved drug formulations may also cause pump damage resulting in pump motor stalls.

Incompatible Formulations with the Infusion System Pumps

Additives, unapproved concentrations, and admixture solutions may alter the material properties of the infusion system components and exhibit chemical properties that are not compatible with the infusion system. This could interfere with the safe and reliable performance of the infusion system. Examples of these include:

- Some antimicrobial preservatives and antioxidant preservatives are known to damage the SynchroMed EL and SynchroMed II infusion systems (e.g., sodium metabisulfite).
- Drug concentrations that require additives to maintain solubility may not be compatible with the infusion system.
- Admixture solutions may result in increased permeation rates of corrosive agents.
- Drug formulations with a pH ≤ 3 are not compatible with the infusion system.
- Higher permeation rates are generally associated with hydrophobic drugs (e.g. fentanyl, bupivacaine).

Compatible Formulations with the Infusion System Pumps

Drug formulations specified in the pump labeling have been tested for compatibility and in-pump stability with the SynchroMed infusion systems. The product labeling contains precise specifications and controls (e.g., concentration, pH, and impurities) to clarify which drug formulations constitute approved versus unapproved drugs and drug concentrations.

In studies performed by Medtronic Neuromodulation, approved drug formulations have shown significantly lower chloride (a corrosive agent) permeation rates, whereas unapproved drug formulations have shown a wide range of chloride permeation rates, with some unapproved drug formulations showing a level of chloride permeation rates orders of magnitude higher than for approved drugs.

Conclusion

Use only those drugs and drug formulations for which the SynchroMed infusion system is approved to minimize the potential for damage to the internal pump components. The use of unapproved drug formulations can increase the risk of pump motor stall due to corrosion in the SynchroMed infusion systems. Be aware that even if an approved drug formulation is currently being used, previous use of an unapproved drug formulation in that pump may have already increased the risk of corrosion leading to a permanent motor stall.

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Summary of Approved Drugs

SynchroMed® II Infusion System

For complete information, refer to the *Indications, Drug Stability, and Emergency Procedures* reference manual, product labeling number MA12510A012

Physicians prescribing the SynchroMed II Infusion System for use with the drugs listed below must be familiar with the indications, contraindications, warnings, precautions, adverse events, dosage and administration information, and screening procedures described in the drug labeling. Each system includes (at a minimum) a pump and a catheter.

Warning: Nonindicated formulations (including drugs not listed below, admixtures, compounded drugs, and unapproved drug concentrations) are not approved for use or tested with the infusion system. Use of nonindicated drugs or fluids can result in increased risks to the patient, damage to the infusion system requiring surgical replacement, and a loss or change in therapy, which may lead to a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug underdose.

Drugs for which the SynchroMed II Infusion System is approved

(Reference MA12510A012 pages 29-31)

The chronic epidural/intrathecal infusion of preservative-free morphine sulfate (or morphine hydrochloride) sterile solution in the treatment of chronic intractable pain. The maximum approved concentration is 25 mg/mL.

- A 0.9% solution of preservative-free sodium chloride injection can be used to achieve the physician-prescribed concentration of preservative-free morphine sulfate (or morphine hydrochloride) sterile solution.

The chronic intrathecal infusion of baclofen injection in the management of severe spasticity. The maximum approved concentration is 2 mg/mL.

- A 0.9% solution of preservative-free sodium chloride injection can be used to achieve the physician-prescribed concentration of Lioresal Intrathecal (baclofen injection).

The chronic intrathecal infusion of preservative-free ziconotide sterile solution for the management of severe chronic pain. The maximum approved concentration is 100 µg/mL.

- A 0.9% solution of preservative-free sodium chloride injection can only be used with preservative-free ziconotide sterile solution after the initial fill of the pump with this drug.

The chronic intravascular infusion of floxuridine (FUDR) for the treatment of primary or metastatic cancer.

- Bacteriostatic water or preservative-free sterile saline can be used to achieve the physician prescribed concentration of chemotherapy drugs or to flush the pump reservoir. Saline or heparinized physiological saline (unless contraindicated) may be used during an interruption in chemotherapy to maintain pump and catheter patency.

The chronic intravascular infusion of methotrexate for the treatment of primary or metastatic cancer.

- Bacteriostatic water or preservative-free sterile saline can be used to achieve the physician prescribed concentration of chemotherapy drugs or to flush the pump reservoir. Saline or heparinized physiological saline (unless contraindicated) may be used during an interruption in chemotherapy to maintain pump and catheter patency.