To addressee only

John Sample
Sample Pharmaceuticals
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18th June 2014

Dantrolene sodium (DANTRIUM® Intravenous): use a filter needle to draw up reconstituted solution from new stock until further notice

Dear Healthcare Professional,

We are writing to inform you of the following:

Summary

- Some vials of dantrolene sodium for intravenous use may contain visible particles after reconstitution. These particles are crystals of dantrolene sodium.
- All newly released packs of dantrolene sodium are being supplied with one blunt filter needle per vial (a BD Blunt Fill Needle with 5 micron filter 18 G 40 mm).
- Reconstituted dantrolene sodium from newly released stock must be drawn up with this blunt filter needle to remove the undissolved crystals prior to administration to patients.
- If the solution is not filtered, the administered crystals may result in an increased risk of injection site reactions including erythema, rash, swelling, localized pain, thrombophlebitis, and tissue necrosis.
- Filtering does not affect the amount of intravenous dantrolene in solution; no reduction in efficacy of the filtered solution is anticipated.
- Existing stock is not affected and does not require filtering.
- Stickers with filtering instructions are included with this letter. Place these stickers on to emergency toolkits for the treatment of malignant hyperthermia.

Further Information

Dantrolene sodium is indicated for the treatment of malignant hyperthermia. Due to a manufacturing issue, some vials of dantrolene sodium may contain undissolved dantrolene sodium crystals after reconstitution. The emergency measures outlined in this letter are to ensure continued supply of dantrolene sodium until the manufacturing problem is resolved. These measures apply immediately and until further notice.

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Instructions for reconstitution

1. Reconstitute the vial with 60 mL of water for injection.
2. Filter the reconstituted product with a blunt fill needle when drawing the solution up into the syringe. Use a BD Blunt Fill Needle with 5 micron filter 18 G 40 mm (provided with newly released stock).
3. Remove the blunt fill needle from the syringe before attaching the syringe to an intravenous cannula or giving set. Discard the blunt fill needle and product vial in an approved sharps collector.
4. Administer the dantrolene sodium solution immediately once reconstituted.
5. Use a new filter needle with every vial of dantrolene sodium.

Reconstitution should be performed in accordance with local infection control guidelines.

Dose
The use of the filter does not reduce the amount of intravenous dantrolene in solution; therefore no reduction in efficacy of the filtered solution is anticipated. Intravenous dantrolene should be administered as currently recommended.

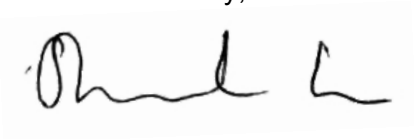
The product information states that the initial dantrolene sodium dose should be 1 mg/kg. If the physiological and metabolic abnormalities persist or reappear, this dose may be repeated up to a cumulative dose of 10 mg/kg. If a relapse or recurrence occurs, dantrolene sodium should be re-administered at the last effective dose.

Risk of skin reactions
Dantrolene sodium is known to be associated with a risk of injection site reactions including erythema, rash, swelling, localized pain, thrombophlebitis, and tissue necrosis. This risk may be increased if the filter is not used to remove the particles from affected vials prior to administration to patients. Therefore, please use the filter needles provided to draw up reconstituted dantrolene sodium solution. Please be vigilant for and report any injection site reactions.

Call for Reporting
Healthcare professionals should report adverse reactions and medication errors in accordance with the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

Should you have any questions or require additional information, please call 0080012002222. This information has been approved for distribution by the EMA (European Medicines Agency), the MHRA and Norgine.

Yours Sincerely,



Dr Sharmila Kar
Medical Director UK and Ireland

UK - UK/DIV/0614/0009

PRESCRIBING INFORMATION: DANTRIUM® Intravenous 20mg powder for solution for injection

REFER TO FULL SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) BEFORE PRESCRIBING

Presentation: Each box contains 12 or 36 vials. Each vial contains 20mg dantrolene sodium formulated as powder for solution for injection to be reconstituted with 60ml of Water for injections.

Indications: Treatment of malignant hyperthermia (MH).

Dosage and administration: As soon as MH is recognised, all anaesthetic agents should be discontinued. An initial dose of 1mg/kg should be given rapidly into the vein. This dose may be repeated up to a cumulative dose of 10 mg/kg. Clinical experience has shown that the average dose of DANTRIUM IV required has been 2.5 mg/kg. If a relapse or recurrence occurs, DANTRIUM IV should be re-administered at the last effective dose.

Special warnings and precautions: In some subjects, as much as 10 mg/kg of DANTRIUM IV has been needed to reverse MH. The 3000mg of mannitol present in each vial of DANTRIUM IV should be taken into consideration when calculating total mannitol dose for the prevention or treatment of renal complications of MH. Care must be taken to prevent extravasation of the intravenous solution. The use of DANTRIUM IV in the management of MH is not a substitute for supportive measures. Whilst the licensed indications of intravenous dantrolene sodium do not generally necessitate prolonged therapy, the risk of hepatic dysfunction may increase with dose and duration of treatment, based on experience with oral therapy. However in some patients it is of an idiosyncratic of hypersensitivity type, and could occur after a single dose. DANTRIUM IV should not be mixed with other intravenous infusions.

Interactions: It is recommended that the combination of DANTRIUM IV and calcium channel blockers, such as verapamil, is not used during the reversal of a MH crisis. Administration of dantrolene may potentiate vecuronium-induced neuromuscular block.

Pregnancy and lactation: The safety of DANTRIUM IV in pregnant women has not been established. DANTRIUM IV should only be given during pregnancy when the potential benefits outweigh the possible risk to mother and child. Use in nursing mothers only if the potential benefit justifies the potential risk to the infant.

Effects on ability to drive and use machines: Patients must not operate an automobile or engage in other hazardous activity for up to 48 hours.

Side-effects: There have been occasional reports of death following MH crisis even when treated with intravenous dantrolene sodium. There have been rare reports of pulmonary oedema developing during the treatment. Injection site reactions, thrombophlebitis, extravasation and hepatic dysfunction may occur, including fatal hepatic failure. Refer to SmPC for full product information and list of side-effects.

MA: PL 34413/0003.

MA Holder: SpePharm Holding B.V., Kingsfordweg 151, 1043 GR Amsterdam, The Netherlands.

Legal category: POM.

NHS Price: 12 X 20mg £612; 36 X 20mg £1,836.

Date of revision: DA/3714/SEP/13

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard

Adverse events should also be reported to SpePharm on 0844 800 7579