1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

DANTRIUM VIALS 20 mg (powder for solution for injection)

COMPOSITION

Each 70 ml vial of DANTRIUM VIALS 20 mg contains 20 mg dantrolene sodium.

Excipients:

Mannitol, sodium hydroxide

Contains sugar: Mannitol 3 g

CLASS AND CATEGORY

A 17.1 Peripherally acting muscle relaxants

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Dantrolene sodium is a muscle relaxant acting specifically on skeletal muscle. It does not affect neuromuscular transmission nor does it have measurable effects on the electrically excitable surface membrane. Studies show that in the presence of dantrolene sodium, the responses of the muscle to caffeine are decreased or delayed.

In isolated muscle preparations, dantrolene sodium uncouples the excitation and contraction of skeletal muscle probably by interfering with the release of calcium from the sarcoplasmic

reticulum.

In the anaesthetic-induced malignant hyperthermia syndrome, evidence points to an intrinsic abnormality of muscle tissue, in affected humans and swine, it has been postulated that “triggering agents” induce a sudden rise in myoplasmic calcium either by preventing the sarcoplasmic reticulum from accumulating calcium adequately or by accelerating its release. This rise in myoplasmic calcium activates acute catabolic processes common to the malignant hyperthermia crisis.

Dantrolene sodium may prevent the increase in myoplasmic calcium and the acute catabolism within the muscle cell by interfering with the release of calcium from the sarcoplasmic reticulum to the myoplasm. Thus, the physiologic, metabolic and biochemical changes associated with the crisis may be reversed or attenuated.

Pharmacokinetic properties

Specific metabolic pathways in the degradation and elimination of dantrolene sodium in humans never have been established. Dantrolene is found in measurable amounts in blood and urine. In addition its major metabolites in body fluids are the 5-hydroxy analogue and the acetamido analogue. Another metabolite with an unknown structure appears related to acetylamino-dantrolene. Dantrolene sodium may also undergo hydrolysis and subsequent oxidation forming nitrophenylfuroic acid.

Since dantrolene sodium is metabolised by the liver, enhancement of its metabolism by other drugs is possible however neither phenobarbital nor diazepam appears to affect dantrolene sodium metabolism.

The mean biologic half-life of dantrolene sodium after intravenous administration is about

5 hours. Based on assays of whole blood and plasma, slightly greater amounts of dantrolene are associated with red blood cells than with the plasma fraction of blood. Significant amounts of dantrolene are bound to plasma proteins, mostly albumin, and this binding is readily reversible. Binding to plasma protein is not significantly altered, by diazepam diphenylhydantoin or phenylbutazone. Binding to plasma proteins is reduced by warfarin and clofibrate and increased by tolbutamide.

In animals, dantrolene sodium given intravenously has no appreciable effect on the cardiovascular system or on respiratory function. A transient inconsistent effect on smooth muscle has been observed at high doses.

INDICATIONS

DANTRIUM VIALS 20 mg intravenous injection is indicated for treatment of malignant hyperthermia. It should be administered by intravenous injection as soon as the malignant hyperthermia reaction is recognised (i.e. tachycardia, tachypnoea central venous desaturation, central venous hypercarbia, metabolic acidosis, fever, skeletal muscle rigidity or cyanosis and mottling of the skin). At the same time it is important to recognise that appropriate supportive measures be instituted for treatment of the physiologic and metabolic abnormalities.

CONTRAINDICATIONS

No known contraindications.

WARNINGS AND SPECIAL PRECAUTIONS

Because of the high pH of the intravenous formulation of DANTRIUM VIALS 20 mg care must be taken to prevent extravasation of the intravenous solution into the surrounding tissues.

Effects on ability to drive and use machines

Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that DANTRIUM VIALS 20 mg does not adversely affect their ability to do so safely.

Excipients

DANTRIUM VIALS 20 mg contains mannitol and may have a laxative effect.

INTERACTIONS

The combination of therapeutic doses of intravenous DANTRIUM VIALS 20 mg and verapamil in halothane α-chloralose anaesthetised swine has resulted in ventricular fibrillation and cardiovascular collapse in association with marked hyperkalaemia. It is recommended that the combination of intravenous DANTRIUM VIALS 20 mg and calcium channel blockers, such as verapamil not be used during reversal of a malignant hyperthermia crisis until the relevance of these findings to humans is established.

HUMAN REPRODUCTION

The safety of DANTRIUM VIALS 20 mg in women who are or who may become pregnant has not been established: it should be given only when the potential benefits have been weighed against the possible risk to mother and child.

DOSAGE AND DIRECTIONS FOR USE

As soon as the malignant hyperthermia reaction is recognized, all anaesthetic agents should be discontinued. An initial DANTRIUM VIALS 20 mg intravenous dose of 1 mg/kg should be given rapidly. If the physiologic and metabolic abnormalities persist, or reappear, this dose may be repeated up to a cumulative dose of 10 mg/kg. Based on clinical experience to date, reversal of the manifestations of malignant hyperthermia may be achieved with an average cumulative

dose of 2,5 mg/kg of DANTRIUM VIALS 20 mg. However it is recommended that 36 vials (720 mg) are available which would provide a dosage of 10 mg/kg body mass for patients with body mass up to 70 kg.

Each vial of DANTRIUM VIALS 20 mg should be reconstituted by adding 60 ml of water for injection and the vial shaken until the solution is clear. The contents of the vial must be **protected from the direct light** and **used within 6 hours** after reconstitution, because being a hydantoin, dantrolene sodium may form hydrate in aqueous solution, which has lesser solubility than the dantrolene salt and may occasionally precipitate. This has never been found before 6 hours: protect the reconstituted solutions from temperatures above 30 °C (86 °F) and below 15 °C (59 °F).

USE OF THE BBraun FILL NEEDLES WITH FILTER

The filter needle provided with this product is intended for use when drawing reconstituted DANTRIUM VIALS 20 mg solution from the vial into the syringe prior to administration to the patient. The filter needle then needs to be **exchanged** for an appropriate intravenous cannula or giving set and MUST NOT be used to administer the product to the patient.

Instructions:

1) Reconstitute the vial with 60 ml of water for injection.
2) Filter the reconstituted product with the BBraun fill needle with filter provided when drawing up the solution into the syringe.
3) Remove the BBraun fill needle from the syringe prior to attachment to an intravenous cannula or giving set.
4) Discard the BBraun fill needle and product vial in an approved sharps collector.
5) Not for skin injection.
6) Use a new filter needle with every vial of DANTRIUM VIALS 20 mg.

7) Administer DANTRIUM VIALS 20 mg immediately upon reconstitution.

SIDE EFFECTS

The serious reactions reported with chronic oral DANTRIUM use have been hepatitis, seizures and pleural effusion with pericarditis. Hypersensitivity with attendant skin reactions reported in patients treated taking oral DANTRIUM, has been reported in patients treated with short-term DANTRIUM VIALS 20 mg intravenous therapy for malignant hyperthermia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

No overdosage has to date occurred.

IDENTIFICATION

Compact, slightly orange-yellow mass, filling ca. 2/3 of vial volume.

PRESENTATION

1 x 70 ml clear Type 1, glass vial, with an aluminium crimping cap Type 1 siliconized grey bromo-butyl rubber stopper and a polypropylene flip-off disk, together with a BBraun filter needle.

1 vial is packed in an outer cardboard carton together with a leaflet.

STORAGE INSTRUCTIONS

Store the unopened vials in a cool, dark place. The contents of the vial must be **protected from direct light** and **used within 6 hours** after reconstitution. Protect the reconstituted solutions from temperatures above 30 °C and below 15 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

M/17.1/253

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

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