NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Dantrium® IV 20 mg powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 65 mL vial contains 20 mg dantrolene sodium hemiheptahydrate, 3 g mannitol and sufficient sodium hydroxide to yield a pH of approximately 9.5 when reconstituted with 60 mL of sterile water for injections (without a bacteriostatic agent).

Dantrolene sodium is classified as a direct-acting skeletal muscle relaxant. Chemically, the drug is hydrated 1-[[[5-(4-nitrophenyl)-2-furanyl]methylene]-amino]-2,4-imidazolidinedione sodium salt. The hydrated salt contains approximately 15% water (3½ moles) and has a molecular weight of 399. The anhydrous salt has a molecular weight of 336.

Excipient(s) with known effect

- Sodium hydroxide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for injection.

Dantrium powder for injection is a sterile lyophilised formulation of dantrolene sodium, and in this form provides a preparation for intravenous use.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dantrium for injection is indicated, along with appropriate supportive measures, for the management of the fulminant hypermetabolism of skeletal muscle characteristic of malignant hyperthermia crisis. It should be administered by intravenous injection as soon as the malignant hyperthermia reaction is recognised (i.e. tachycardia, tachypnea, central venous desaturation, hypercarbia, metabolic acidosis, skeletal muscle rigidity, increased utilisation of anaesthesia circuit carbon dioxide absorber, cyanosis and mottling of the skin, and, in many cases, fever).

4.2 Dose and method of administration

Dose

As soon as the malignant hyperthermia reaction is recognised, all anaesthetic agents should be discontinued. Dantrium for injection should be administered by continuous rapid intravenous push beginning at a minimum dose of 1 mg/kg, and continuing until symptoms

subside or the maximum cumulative dose of 10 mg/kg has been reached. If the physiologic and metabolic abnormalities reappear, the regimen may be repeated.

It is important to note that administration of Dantrium for injection should be continuous until symptoms subside. The effective dose to reverse the crisis is directly dependent upon the individual's degree of susceptibility to malignant hyperthermia, the amount and time of exposure to the triggering agent, and the time elapsed between onset of the crisis and initiation of treatment.

Special populations

Paediatric population

Experience to date indicates that the dose for children is the same as for adults.

Preparation

Each vial of Dantrium for injection should be reconstituted by adding 60 mL of sterile water for injections (without a bacteriostatic agent), and the vial shaken until the solution is clear. The contents of the vial must be protected from direct light and used within 6 hours after reconstitution. Store reconstituted solutions at controlled room temperature (15^oC – 25^oC). Store unreconstituted product below 25^oC and avoid prolonged exposure to light.

4.3 Contraindications

None.

4.4 Special warnings and precautions for use

The use of Dantrium for injection in the management of malignant hyperthermia crisis is not a substitute for previously known supportive measures. These measures must be individualised, but it will usually be necessary to discontinue the suspect triggering agents, attend to increased oxygen requirements, manage the metabolic acidosis, institute cooling when necessary, attend to urinary output, monitor for electrolyte imbalance.

General

Because of the high pH of the intravenous formulation of Dantrium and potential for tissue necrosis, care must be taken to prevent extravasation of the intravenous solution into the surrounding tissues.

When mannitol is used for prevention or treatment of late renal complications of malignant hyperthermia, the 3 g of mannitol needed to dissolve each 20 mg vial of Dantrium for injection should be taken into consideration.

Caution is also indicated at meals on the day of administration because difficulty in swallowing and choking has been reported.

Hepatotoxicity

Although less likely to occur with Dantrium for injection given short-term for life-threatening malignant hyperthermia, hepatic dysfunction, including fatal hepatic failure, can occur with dantrolene use, and is related to dose and duration of therapy.

With dantrolene sodium capsules*:* Dantrolene sodium has a potential for hepatotoxicity and should not be used in conditions other than those recommended. Symptomatic hepatitis (fatal and non-fatal) has been reported at various dose levels of the drug. The incidence reported in patients taking up to 400 mg/day is much lower than in those taking doses of 800 mg or more per day. Even sporadic short courses of these higher dose levels within a treatment regimen markedly increased the risk of serious hepatic injury. Liver dysfunction as evidenced by blood chemical abnormalities alone (liver enzyme elevations) has been observed in patients exposed to dantrolene sodium for varying periods of time. Overt hepatitis has occurred at varying intervals after initiation of therapy, but has been most frequently observed between the third and twelfth month of therapy. The risk of hepatic injury appears to be greater in females, in patients over 35 years of age and in patients taking other medication(s) in addition to dantrolene sodium. Dantrolene sodium should be used only in conjunction with appropriate monitoring of hepatic function including frequent determination of SGOT and SGPT.

Fatal and non-fatal liver disorders of an idiosyncratic or hypersensitivity type may occur with dantrolene sodium therapy.

4.5 Interaction with other medicines and other forms of interaction

The combination of therapeutic doses of intravenous dantrolene sodium and verapamil in halothane/alpha-chloralose anaesthetised swine has resulted in ventricular fibrillation and cardiovascular collapse in association with marked hyperkalaemia. Myocardial depression and hyperkalaemia have also been reported rarely in malignant hyperthermia-susceptible patients receiving intravenous dantrolene and concomitant calcium channel blockers. It is recommended that the combination of intravenous dantrolene sodium and calcium channel blockers, such as verapamil, not be used during reversal of a malignant hyperthermia crisis.

Administration of dantrolene may potentiate the effects of non-depolarising muscle relaxants such as vecuronium.

Caution should be exercised in the concomitant administration of tranquillising agents. Dantrolene causes dizziness, drowsiness, and weakness; alcohol and other CNS depressants may intensify this effect.

4.6 Fertility, pregnancy and lactation

Fertility

No data available.

Pregnancy - Category B2

The safety of Dantrium for injection 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. Dantrolene crosses the placenta.

Lactation

No data are available concerning the use of dantrolene sodium in nursing mothers. Dantrolene has been detected in human breast milk.

4.7 Effects on ability to drive and use machinery

Adverse effects such as a decrease in grip strength and weakness of leg muscles, especially walking down stairs, can be expected postoperatively. In addition, lightheadedness, dizziness and drowsiness may persist for up to 48 hours after treatment and patients must not operate an automobile or engage in other hazardous activity during this time.

4.8 Undesirable effects

There have been occasional reports of death following malignant hyperthermia crisis even when treated with intravenous dantrolene sodium. Most of these deaths can be accounted for by late recognition, delayed treatment, inadequate dosage, lack of supportive therapy, intercurrent disease and/or development of delayed complications such as renal failure or disseminated intravascular coagulopathy. In some cases, there are insufficient data to completely rule out therapeutic failure of dantrolene sodium.

There are rare reports of fatality in MH crisis, despite initial satisfactory response to intravenous dantrolene sodium, which involve patients who could not be weaned from dantrolene sodium after initial treatment.

The administration of intravenous dantrolene sodium to human volunteers is associated with loss of grip strength and weakness in the legs, as well as drowsiness and dizziness.

There are rare reports of pulmonary oedema developing during the treatment of MH crisis in which the diluent volume and mannitol needed to deliver intravenous dantrolene sodium possibly contributed.

Thrombophlebitis has been observed distant from the injection site, and also rarely as a systemic manifestation following administration of dantrolene sodium.

Injection site reactions, extravasations and phlebitis are commonly reported. Systemic urticaria and erythema are very infrequently reported with Dantrium for injection, seldom as the primary event but more commonly as manifestations of injection site reactions.

The serious reactions reported with chronic oral Dantrium use have been hepatitis, seizures, and pleural effusion with pericarditis. None of the reactions reported in patients taking oral Dantrium have been reported in patients treated with short-term Dantrium for injection therapy for malignant hyperthermia.

The following additional events have been reported in patients receiving oral dantrolene: abdominal cramps, abnormal hair growth, acne-like rash, anorexia, alteration of taste, aplastic

anaemia, anaphylaxis, backache, chills, constipation rarely progressing to signs to intestinal obstruction, crystalluria, diarrhoea, difficult erection, difficult urination and/or urinary retention, diplopia, eczematoid eruption, erratic blood pressure, exacerbation of cardiac insufficiency, excessive tearing, fatigue, feeling of suffocation, fever, gastric irritation, general malaise, myalgia, GI bleeding, haematuria, headache, heart failure, increased nervousness, increased urinary frequency, insomnia**,** leucopenia, light-headedness, liver function test disturbances, lymphocytic lymphoma, mental confusion, mental depression, nausea, phlebitis, pruritus, speech disturbance, swallowing difficulty, sweating, tachycardia, transient lowering of G.F.R. and renal plasma flow after 8 weeks' therapy has been reported, urinary incontinence and/or nocturia, urticaria, visual disturbance, and vomiting.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Fatal poisoning with this agent is rare, and lethal doses are not established. There is no known set of symptoms with acute overdose. Signs and symptoms are likely to be an extension of those under section 4.8. The primary toxic effect is CNS depression and in severe cases coma. Respiratory depression may occur in patients with significant CNS depression. Total skeletal paralysis is unlikely in conscious patients. Symptoms which may occur in case of overdose include, but are not limited to, muscular weakness and alterations in the state of consciousness (e.g. lethargy, coma), vomiting, diarrhoea and crystalluria. Mild tachycardia and hypotension may develop.

Monitor and support respiratory and cardiovascular function.

Intravenous fluids should be administered in fairly large quantities to avert the possibility of crystalluria. Consider central venous pressure monitoring to guide further fluid therapy. Fluids and electrolytes should be monitored closely. Monitor patients with significant CNS depression for respiratory insufficiency and rhabdomyolysis.

Excretion of the active compounds is NOT known to be enhanced by fluid diuresis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxants, directly acting agents, ATC code: M03CA01

Mechanism of action

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 have shown 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.

5.2 Pharmacokinetic properties

Specific metabolic pathways in the degradation and elimination of dantrolene sodium in humans 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 phenobarbitone 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 muscles has been observed at high doses.

Because of the low drug concentration requiring the administration of large volumes of fluid, acute toxicity of a dantrolene sodium intravenous formulation could not be assessed. In 14-day (subacute) studies, the intravenous formulation of dantrolene sodium was relatively non-toxic to rats at doses of 10 mg/kg/day and 20 mg/kg/day. While 10 mg/kg/day in dogs for 14 days evoked little toxicity, 20 mg/kg/day for 14 days caused hepatic changes of questionable biologic significance.

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Mannitol
- Sodium hydroxide

6.2 Incompatibilities

No data available.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25ºC.

6.5 Nature and contents of container

Dantrium powder for injection 20 mg glass vials, in packs of 6's.

Please Note: In some subjects as much as 10 mg/kg of dantrolene sodium has been needed to reverse MH. In a 70 kg man this dose would require about 36 vials. Such a volume has been administered in approximately 90 minutes.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand
Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

10 December 1979

10. DATE OF REVISION OF THE TEXT

22 December 2020

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.3	Update to shelf life.