SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dantrium Intravenous 20 mg Powder for Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 20 mg dantrolene sodium. After reconstitution the solution contains 0.33 mg/ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

A pale orange to yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of malignant hyperthermia.

4.2 Posology and method of administration

Posology
As soon as the MH reaction is recognised, all anaesthetic agents should be discontinued; the administration of 100 % oxygen is recommended. Dantrium Intravenous 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 Intravenous should be continuous until symptoms subside. The effective dose to reverse the crisis is directly dependent upon the individual's degree of susceptibility to MH, the amount and time of exposure to the triggering agent, and the time elapsed between onset of the crises and administration of treatment.

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

Method of administration
Dantrium 20 mg powder for solution is available for intravenous administration only.
For instructions on use reconstitution of the medical product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to dantrolene sodium or to any of the excipients listed in 6.1

4.4 Special warnings and precautions for use

The use of Dantrium Intravenous in the management of MH crisis is not a substitute for other 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, monitor urinary output, and monitor for electrolyte imbalance.

Since the effect of disease state and other drugs on dantrolene sodium related skeletal muscle weakness, including possible respiratory depression, cannot be predicted, patients who receive IV dantrolene sodium preoperatively should have vital signs monitored.

If patients judged with MHS are administered intravenous or oral dantrolene sodium preoperatively, anaesthetic preparation must still follow a standard MHS regimen, including the avoidance of known triggering agents. Monitoring for early clinical and metabolic signs of MH is indicated because attenuation of MH, rather than prevention, is possible. These signs usually call for the administration of additional IV dantrolene sodium.

When mannitol is used to prevent or treat the renal complications of malignant hyperthermia, the mannitol content in the Dantrium vial, i.e. 3000 milligrams of mannitol per 20mg of dantrolene sodium, should be taken into consideration.

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

In some subjects as much as 10mg/kg of dantrolene sodium has been needed to reverse the crisis. In a 70 kg man this dose would require approximately 36 vials. Such a volume has been administered in approximately one and a half hours.

Information for Patients
Based upon data in human volunteers, it will sometimes be appropriate to tell patients who receive dantrolene sodium intravenous that decrease in grip strength and weakness of leg muscles, especially walking down stairs, can be expected postoperatively. Caution is also indicated at meals on the day of administration because difficulty in swallowing and choking has been reported. Caution should be exercised in the concomitant administration of tranquilizing agents.

Hepatotoxicity seen with dantrolene sodium capsules
Dantrolene has a potential for hepatotoxicity, and symptomatic hepatitis, sometimes fatal, has been reported. Factors that may be related to a poorer prognosis include higher daily doses, prolonged duration of therapy, female gender, and increasing patient age. Spontaneous reports also suggest a higher proportion of hepatic events with fatal outcome in elderly patients.

Hepatic dysfunction, including fatal hepatic failure, can occur with dantrolene use, and appears to be related to dose and duration of therapy. Fatal and non-fatal liver disorders of idiosyncratic or hypersensitivity type may also occur with dantrolene sodium therapy.

Evaluation of hepatic function should be done before initiating treatment, and hepatic function should be monitored at appropriate intervals throughout treatment. If monitoring reveals abnormal liver function, or if signs or symptoms of hepatotoxicity occur during therapy, dantrolene should be withdrawn. If a decision is made to restart treatment after recovery from hepatic dysfunction, liver function should be monitored and the drug discontinued if abnormal values are observed.

4.5 Interaction with other medicinal products and other forms of interaction

Dantrolene is metabolised by the liver, and it is theoretically possible that its metabolism may be enhanced by drugs known to induce hepatic microsomal enzymes. However, neither phenobarbital nor diazepam appears to affect dantrolene's metabolism. 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.

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.

Hyperkalaemia and myocardial depression have also been reported rarely in malignant hyperthermia-susceptible patients receiving intravenous dantrolene sodium and concomitant calcium channel blockers. Hence, the use of Dantrium Intravenous and calcium channel blockers in combination is not recommended, until the relevance of these findings to humans is established.

Administration of dantrolene may potentiate vecuronium-induced neuromuscular block.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of Dantrium Intravenous in pregnant women has not been established: Dantrolene crosses the placenta, and should be given only when the potential benefits have been weighed against the possible risk to mother and child.

Breast feeding
Dantrolene has been detected in human milk at low concentrations (less than 2 micrograms per milliliter) during repeat intravenous administration over 3 days. Dantrium Intravenous should be used by nursing mothers only if the potential benefit justifies the potential risk to the infant.

Fertility
There are no data on the effects of Dantrium on fertility in humans.

4.7 Effects on ability to drive and use machines

A decrease in grip strength and weakness of leg muscles, especially walking down stairs, can be expected postoperatively. In addition, symptoms such as "light headedness" may be noted. Since some of these symptoms may persist for up to 48 hours, patients must not operate an automobile or engage in other hazardous activity during this time.

4.8 Undesirable effects

Summary of the safety profile

There have been occasional reports of death following MH crisis even when treated with intravenous dantrolene. Incidence figures are not available (the pre-dantrolene mortality of MH crisis was approximately 50 %). Most of these deaths can be accounted for by late recognition, delayed treatment, inadequate dosage, lack of supportive therapy, intercurrent disease and/or the 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.

There are rare reports of fatality in MH crisis, despite initial satisfactory response to Dantrium Intravenous, which involve patients who could not be weaned from dantrolene after initial treatment. The administration of intravenous dantrolene to human volunteers is associated with loss of grip strength and weakness in the legs, as well as subjective CNS complaints.

The following adverse reactions are in approximate order of severity:

System Organ Class	Frequency	Adverse Drug Reaction
Blood and lymphatic disorders	Unknown	Thrombophlebitis
Immune system disorder	rare	Anaphylaxis
Nervous system disorders	Unknown	Dizziness, somnolence, convulsion, speech disorder
Cardiac disorders	Unknown:	Cardiac failure, bradycardia, tachycardia
Respiratory, thoracic and mediastinal disorders	Rare Unknown:	Pulmonary oedema Pleural effusion, respiratory failure, respiratory depression
Gastrointestinal disorders	Unknown	Abdominal pain, nausea, vomiting, gastrointestinal bleeding
Hepatobiliary disorders	Unknown:	jaundice, hepatitis
Skin and subcutaneous disorders	Rare Unknown:	Urticaria, erythema Hyperhidrosis
Renal and urinary disorders	Unknown:	Crystalluria
General disorders and administration site conditions	common	Local injection site reactions

For orally administered dantrolene sodium the unwanted effects associated with the use of Dantrium are as follows:

System Organ Class	Frequency	Adverse Drug Reaction
Metabolism and nutrition disorders	Common	Anorexia
Psychiatric disorders:	Less common	Mental depression, mental confusion
Nervous system disorders:	Common	Seizure, speech disturbance, headache, drowsiness, dizziness
Eye disorders	Common	Visual disturbances
Cardiac disorders	Common Less common	Pericarditis Exacerbation of cardiac insufficiency, tachycardia
Vascular disorders	Less common	Labile blood pressure

Respiratory, thoracic and mediastinal disorders	Common: Less Common	Pleural effusion with associated eosinophilia, respiratory depression Dyspnoea
Gastrointestinal disorders	Common Less common	Nausea and/or vomiting, abdominal pain, diarrhoea Swallowing difficulties, constipation (rarely progressing to signs of intestinal obstruction)
Hepato-biliary disorders	Common	Hepatotoxicity (see section 4.4), liver function test disturbances
Skin and subcutaneous tissue disorders	Common Less common	Acne-like rash, skin eruptions Sweating
Renal and urinary disorders	Less common	Incontinence, increased urinary frequency, urinary retention, haematuria, crystalluria
General disorders and administration site conditions	Common Common	weakness, general malaise, fatigue Chills and /or fever

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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.

For acute overdose, general supportive measures should be employed.

Intravenous fluids should be administered in fairly large quantities to avert the possibility of crystalluria. An adequate airway should be maintained and artificial resuscitation equipment should be at hand.

Electrocardiographic monitoring should be instituted, and the patient carefully observed. The value of dialysis in dantrolene sodium overdose is not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: M03CA01, muscle relaxants, directly acting agents.

Mechanism of action

Dantrolene is classified as a direct-acting skeletal muscle relaxant. In isolated nerve-muscle preparation, dantrolene sodium has been shown to produce relaxation by affecting the contractile response of the skeletal muscle at a site beyond the myoneural junction, directly on the muscle itself.

Pharmacodynamic effects
In skeletal muscle, dantrolene dissociates the excitation-contraction coupling, probably by interfering with the release of Ca^{++} from the sarcoplasmic reticulum. This effect appears to be more pronounced in fast muscle fibres as compared to slow ones, but generally affects both.

Clinical efficacy and safety
A central nervous system effect occurs, with drowsiness, dizziness, and generalised weakness occasionally present. Although dantrolene does not appear to directly affect the CNS, the extent of its indirect effect is unknown.

5.2 Pharmacokinetic properties

Metabolism
Specific metabolic pathways for the degradation and elimination of dantrolene in humans have been established. Dantrolene is found in measurable amounts in blood and urine.

Its major metabolites in body fluids are 5-hydroxy dantrolene and an acetylamino metabolite of dantrolene. Another metabolite with an unknown structure appears related to the latter. Dantrolene may also undergo hydrolysis and subsequent oxidation forming nitrophenylfuroic acid.

Elimination
The mean biologic half-life of dantrolene after intravenous administration is variable, between 4 to 8 hours under most experimental conditions. 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.

5.3 Preclinical safety data

Carcinogenicity
Dantrolene sodium showed some evidence of tumourgenicity at high dose levels in Sprague-Dawley female rats. These effects were not seen in other studies in Fischer 344 rats or HaM/ICR mice.
There is no clinical evidence of carcinogenicity in humans; however, this possibility cannot be absolutely excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

5% dextrose injection, 0.9% sodium chloride injection and other acidic solutions are not compatible with Dantrium Intravenous and should not be used.

6.3 Shelf life

Unopened: 3 years.

Reconstituted solution: Chemical and physical in-use stability has been demonstrated for 6 hours at 25°c. From a microbiological point of view the product should be used immediately.

6.4 Special precautions for storage

Unopened product: Do not store above 25°C.

Reconstituted solution: Do not store above 25°C. Do not refrigerate or freeze. Protect from direct light.

For storage conditions after reconstitution of the medicinal product, see section 6.3

6.5 Nature and contents of container

Clear 70 ml vials, glass Type I (Ph. Eur.), with siliconised chlorobutyl lyophilisation stoppers Type I (Ph. Eur.). The vials are sealed with aluminium caps with polypropylene flip-off disks. Supplied in packs of 12 or 36 vials.

6.6 Special precautions for disposal and other handling of the product

Reconstitution
Each vial of Dantrium Intravenous should be reconstituted by adding 60 ml of Water for Injection Ph. Eur. and shaking until the solution is clear. Any unused portion of the reconstituted solution should be discarded. There are no special requirements relating to the disposal of the container or contents.

7. MARKETING AUTHORISATION HOLDER

Norgine B.V.
Antonio Vivaldistraat 150, 1083HP Amsterdam The Netherlands

8. MARKETING AUTHORISATION NUMBER

PA 1336/004/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd December 1980

Date of last renewal: 2nd December 2010

10. DATE OF REVISION OF THE TEXT