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 20mg dantrolene sodium. After reconstitution, the solution contains 0.33mg/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

In combination with adequate support measures, Dantrium Intravenous is indicated in adults and children in the treatment of malignant hyperthermia.

4.2 Posology and method of administration

Posology
Dantrium Intravenous should be administered by rapid intravenous injection at least 2.5 mg/kg body weight (8-10 vials in adults). As long as the main clinical symptoms of tachycardia, hypoventilation, sustained hyperacidity (pH and pCO_2 monitoring required) and hyperthermia persist, bolus injection should be repeated. In most cases, a total dose of 10 mg/kg body weight per 24h is sufficient. This dose (10 mg/kg) may need to be exceeded in individual cases. Safe uses up to 40 mg/kg have been described. Based on this experience, higher dosages can be administered in isolated cases if required.

Paediatric population
No dosage adjustment required.

Method of administration
For intravenous administration.

Each vial should be prepared by adding 60 mL of sterile water for injection and the vial shaken until the solution is dissolved.

The reconstituted solution should be filtered using the single use filter provided.

For instructions on reconstitution and filtration of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

The use of Dantrium Intravenous in the management of malignant hyperthermic crisis is not a substitute for other supportive measures.

These must be individually continued in their various forms. Dantrium Intravenous may only be infused **intravenously**. Due to the high pH value of the solution (pH 9.5), extravascular injection/infusion must be avoided as it can lead to tissue necrosis. Due to the risk of vascular occlusion, intraarterial injections must be avoided. Spill of the solution on skin should be avoided. If solution gets on the skin, it must be removed with sufficient water.

In addition, due to the potential for undissolved crystals/particles to appear in the re-constituted product and the subsequent potential risk of exacerbation of injection site reactions/tissue necrosis from crystals within affected vials, use of the filtration device when drawing up the solution is required at all times.

Each vial of Dantrium Intravenous contains 3 g mannitol (for adjustment of isotonic solutions). This amount should be considered if mannitol is used to prevent and treat renal complications related to malignant hyperthermia.

Caution should be exercised if hyperkalaemia symptoms occur (muscular paralysis, ECG changes, bradycardic arrhythmias) or in cases of pre-existing hyperkalaemia (renal insufficiency, digitalis intoxication etc.), as an increase in serum potassium has been demonstrated in animal trials as a result of dantrolene.

Liver damage may occur during dantrolene therapy. This is dependent on the dosage and duration of therapy and may run a lethal course.

This medicine contains less than 1mmol sodium (23mg) per vial that is to say essentially "sodium free.

4.5 Interaction with other medicinal products and other forms of interactions

Isolated case reports and animal studies indicate an interaction between dantrolene and calcium channel blockers, such as verapamil and diltiazem, in the form of heart failure. It is recommended that Dantrium Intravenous and calcium channel blockers should not be used at the same time.

Concomitant administration of Dantrium Intravenous with non-depolarising muscle relaxants such as vecuronium can enhance their effect.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited data from the use of dantrolene in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). 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
No information is available on use of dantrolene during breastfeeding. According to its safety profile, a risk to a breastfed infant cannot be excluded as dantrolene is excreted in breastmilk. Therefore, breastfeeding should be discontinued during administration of Dantrium Intravenous. Based on elimination half-life of dantrolene, breastfeeding can be restarted 60 hours after the last dose.

Fertility
Data on the effects of dantrolene on fertility in humans are not available.

4.7 Effects on ability to drive and use machines

Dantrium Intravenous has major influence on the ability to drive and use machines, as it can lead to weakness, dizziness and light-headedness. This applies particularly in combination with alcohol or other medicines that depress the central nervous system.

4.8 Undesirable effects

Tabulated list of adverse reactions.

Adverse Drug Reactions related to dantrolene sodium are presented below according to system organ class and frequency.

Frequencies are defined according to:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1000 to < 1/100)
Rare (≥ 1/10000 to < 1/1000)
Very rare (< 1/10000)
Not known: frequency could not be estimated due to the present data

System Organ Class	**Frequency**	**Adverse Drug Reaction**
Immune system disorder	Unknown	Allergic reactions, anaphylaxis
Metabolism and nutrition disorders	Unknown	Hyperkalaemia
Nervous system disorders	Unknown	Drowsiness, dizziness, general weakness, somnolence, convulsion, speech disorder, headache
Cardiac disorders	Unknown	Cardiac failure, bradycardia, tachycardia
Vascular disorders	Unknown	Thrombophlebitis
Respiratory, thoracic and mediastinal disorders	Unknown	Pulmonary oedema, Pleural effusion, respiratory failure, respiratory depression
Gastrointestinal disorders	Unknown	Abdominal pain/cramps, nausea, vomiting, gastrointestinal bleeding, diarrhoea
Hepatobiliary disorders	Unknown	Jaundice, hepatitis, hepatic dysfunction including fatal hepatic failure, idiosyncratic or hypertensive liver diseases
Skin and subcutaneous disorders	Unknown	Urticaria, erythema Hyperhidrosis
Musculoskeletal and connective tissue disorders	Unknown	Muscle weakness, muscle fatigue
Renal and urinary disorders	Unknown	Crystalluria
Reproductive system and breast disorders	Unknown	Uterine hypotonia
General disorders and administration site conditions	Unknown	Fatigue, administration site reactions

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 Website: www.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: direct-acting muscle relaxants, ATC code: M03CA01.

Dantrolene decouples nerve impulse and contraction in skeletal muscle probably by interfering with calcium release from the sarcoplasmic reticulum. Its action is specific and has no influence on neuromuscular transmission or any measurable effect on the excitable surface membrane.

In anaesthetic-induced malignant hyperthermia, signs indicate a genetic-related anomaly of the muscle cell. It is assumed that the triggering agents cause a sudden rise in myoplasmic calcium, by increasing its release and preventing storage in the sarcoplasmic reticulum. The resulting increase in myoplasmic calcium leads to hypermetabolism, which is the cause of hyperthermia, metabolic acidosis and other symptoms of malignant hyperthermia.

Dantrolene can prevent acute catabolism within the muscle cell by inhibiting the release of calcium from the sarcoplasmic reticulum within the myoplasm. Thus, the physiologic, metabolic and biochemical changes associated with the crisis can be reversed or attenuated. However, dantrolene therapy can only work when calcium has not yet entirely been emptied from the sarcoplasmic reticulum, i.e. dantrolene should be used as early as possible, provided that muscle perfusion is still adequately assured.

5.2 Pharmacokinetic properties

Distribution
Dantrolene is reversibly bound to plasma albumin; as an in vitro binding constant, a value of 4.3x104M 1 was established. For the transplacental passage of dantrolene, a factor of 0.4 was found.

Metabolism
Metabolism in the liver takes place through microsomal enzymes both via
5-hydroxylation at the hydantoin ring and via reduction of the nitro group to amine with subsequent acetylation.
5-hydroxydantrolene has similar activity to that of the parent substance, while the acetamino dantrolene does not have any muscle relaxant effect.

Elimination
Excretion is mainly renal and biliary, whereby renal excretion takes place,
even in long-term use, at a ratio of 79% 5-hydroxydantrolene, 17% acetylamino-dantrolene and 1 to 4% unchanged dantrolene. Renal clearance (5-OH-dantrolene) is 1.8 to 7.8 L/h.
Following intravenous administration, the average elimination half-life of dantrolene is variable, generally it is between 4 and 8 hours, in a malignant hyperthermia patient it is 12 hours. Pharmacokinetic studies in children have shown an average elimination half-life of approximately 7.4 to 12.6 hours.

5.3 Preclinical safety data

Acute toxicity
Non clinical data for intravenous administration are not available. Following
intraperitoneal administration, the LD50 is around 800 mg/kg body weight in rats (human equivalent dose 129 mg/kg) and following oral administration the LD50 is around 3 g/kg in newborn rats (human equivalent dose 484 mg/kg). No LD50 values could be determined following oral administration to adult animals, due to a lack of mortality.

With subacute intravenous administration of dantrolene at doses of up to 20 mg/kg/day, the sole observations were reduced body weight gain in rats (human equivalent dose 3.2 mg/kg) and hepatic changes in dogs (human equivalent dose 11.1 mg/kg).

Chronic toxicity
In chronic toxicity studies rats, dogs and monkeys oral administration of >30 mg/kg/day (human equivalent dose 4.8 mg/kg, 16.2 mg/kg and 9.6 mg/kg, respectively) for 12 months led to a reduction of growth or body weight gain. Hepatotoxic effects and possibly renal obstruction were observed, which were reversible.

Mutagenicity
Dantrolene yielded positive results in the Ames S. typhyimurium test both in the present and absence of a liver activating system.

Carcinogenicity
Dietary doses of dantrolene sodium in rats at doses of up to 60 mg/kg/day (human equivalent dose 9.6 mg/kg) for to 18 months resulted in increases in benign hepatic lymphatic neoplasms, increased hepatic lymphangiomas and hepatic angiosarcomas, and in females only, an increase in mammary tumours. The relevance of these data for clinical use of dantrolene is not known.

Reproductive toxicity
In male and female adult rats dantrolene up to an oral dose of 45 mg/bodyweight/day (human equivalent dose 7.3 mg/kg/day) did not have any adverse effects on fertility or general reproductive capability Administration of dantrolene to pregnant rabbits (45 mg/kg/day; human equivalent dose 14.5 mg/kg/day) led to increased formation of unilateral or bilateral supernumerary ribs in the pups.

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 bromobutyl rubber stopper and an aluminium cap with a polypropylene flip-off disk.. Each vial is provided with a single use filtration device. Supplied in packs of 12 or 36 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution
Each vial of Dantrium Intravenous should be reconstituted by adding 60 ml of water for injection Ph. Eur. and shaking until the powder is dissolved .

Filter the reconstituted product with the single-use filtration device provided when drawing up the solution into the syringe. The reconstituted solution must be used within 6 hours but filtered immediately before use. Remove the filtration device from the syringe prior to attachment to an intravenous cannula or giving set. Any unused portion of the reconstituted solution should be discarded. Discard the filtration device and product vial in an approved sharps collector. Use a new filtration device with every vial of DANTRIUM Intravenous.

Administer DANTRIUM Intravenous immediately upon filtration.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Only use the filtration device provided

7 MARKETING AUTHORISATION HOLDER

Norgine B.V.

Antonio Vivaldistraat 150
1083 HP Amsterdam
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1336/004/003

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

June 2022