SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dantrium 100 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100mg of dantrolene sodium.
Excipients with known effect: Contains lactose monohydrate 181.0 mg and wheat starch 33.0 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard
Dantrium 100 mg capsules are presented in orange/orange hard capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dantrium capsules are indicated for the treatment of chronic, severe spasticity of skeletal muscle resulting from disorders such as stroke, spinal cord injury, cerebral palsy and multiple sclerosis in adults and children over the age of 5 years old weighing 25 kg or more.

4.2 Posology and method of administration

Each patient should be slowly titrated to the required individual dose. For the individual patient the lowest dose compatible with optimal response is recommended. A recommended dosage increment scale is shown below.

Adults:

Dantrium should be titrated no more rapidly than as per the following schedule:

Week 1: 25mg daily
Week 2: 25 mg twice daily
Week 3: 50 mg twice daily
Week 4: 50 mg three times daily

As soon as the optimal dose is reached, patients should receive their total daily dose divided over 2 to 4 individual doses to achieve as uniform plasma levels as possible and to minimise adverse reactions.

Doses higher than 200 mg should not be administered in long-term therapy with Dantrium. Temporarily, the dose can be gradually increased up to 400 mg per day if pressurised or stressful situations are anticipated in the patient. The increased dose should be titrated as follows:

Week 5: 75 mg three times daily
Week 6: 75 mg four times daily
Week 7: 100 mg four times daily

However, doses above 200 mg per day should not be given for more than 2 months.

Paediatric Population

Dosing table for children over 5 years (upwards of 25 kg body weight). For the individual patient the lowest dose compatible with optimal response is recommended. A recommended dosage titration schedule is provided below.

Week 1: 1 Dantrium 25 capsule once daily
Week 2: 1 Dantrium 25 capsules twice daily
Week 3 1 Dantrium capsule three times daily
Week 4 2 Dantrium capsules twice daily
Week 5 2 Dantrium capsules three times daily
Week 6: 3 Dantrium 25 capsules three times daily

For children weighing 50 kg or more, see dosage for adults.
The dose can be increased gradually up to 200 mg daily.

Dantrium is intended for long-term therapy.
If therapeutic success is still absent after 6-8 weeks of treatment, therapy should be discontinued.

As there is insufficient experience with the use of Dantrium in children under 5 years to assess its tolerability, it should not be used in this patient group.

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in 6.1,
- Hepatic disorders,
- Impaired respiratory function
- Severe impaired cardiac function due to myocardial disease
- In cases where abnormally increased tone is required to allow better function, an upright posture or balance during movement.
- Pregnancy and breastfeeding (see section 4.6)
- Wheat allergy (other than coeliac disease), (see section 4.4).

4.4 Special warnings and precautions for use

Dantrium must be used with caution in the following situations:
In cases of amyotrophic lateral sclerosis or in the presence of bulbar paralytic symptoms, as paresis can be enhanced by Dantrium.
Patients with cardiac disease, especially in patients with myocardial damage and/or cardiac arrhythmias, must receive particular medical surveillance.
Dantrolene leads to mild to severe liver damage in about 9 out of 100,000 treated patients, in whom mortality affects 10-20%.

The risk of liver damage seems to be particularly increased at daily doses higher than 300 mg, during prolonged therapy, in women, in patients over 30 years of age or with a history of liver damage and during concomitant use of other medicinal products that can damage the liver. Liver damage may run a lethal course, especially in elderly patients. In patients suffering from multiple sclerosis, the risk of serious liver damage seems to be further increased.
Before the start and during therapy with Dantrium, liver enzymes must be monitored at regular intervals; in particular, SGOT and SGPT must be monitored frequently. Patients in whom the risk of liver damage is increased must receive particularly close monitoring. If values are outside the norm or if symptoms of liver damage occur, Dantrium must be discontinued.
There are indications that, when liver damage occurs, high serum bilirubin levels correlate to severe progression.

To reduce the risk of liver damage, the lowest possible effective dantrolene dose must be used.

Dantrium can cause photosensitisation; patients should therefore protect themselves against strong sunlight during treatment.

Dantrium must be discontinued if patients have developed pleural or pericardial effusion or pleuropericarditis.

Patients with rare hereditary problems of galactose intolerance, the lactase deficiency or glucose-galactose malabsorption should not take Dantrium.

At doses above 200 mg dantrolene per day, increased adverse reactions must be anticipated.

This medicine contains only very low levels of gluten (from wheat starch). It is regarded as 'gluten-free' and is very unlikely to cause problems in case of coeliac disease.

One capsule contains no more than 3.3 micrograms of gluten.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant intake of CNS depressants (such as benzodiazepine-type tranquillisers, antihistamines, sedatives) and alcohol consumption should be avoided, as the adverse reactions to Dantrium may be increased (particularly the depressant effect on the central nervous system and muscle weakness).

With concomitant administration of:
-oestrogens or other potentially hepatotoxic substances, there is an increased risk of liver damage.
-Dantrium and non-depolarising muscle relaxants (vecuronium), its effect can be enhanced.
-metoclopramide, the rate and speed of dantrolene absorption may be increased and thus lead to an increase in the effect and undesirable effects of dantrolene.

In patients predisposed to malignant hyperthermia who were receiving intravenous dantrolene, it was observed that co-administration of calcium antagonists and/or beta-blockers led to hyperkalaemia and heart failure.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of dantrolene sodium in pregnant women. Dantrolene crosses the placenta and can induce muscle hypotonia, especially in the uterus. Studies in animals are insufficient with respect to reproductive *toxicity* (see section 5.3). The use of Dantrium during pregnancy is contraindicated.

Breastfeeding
Dantrium is contraindicated during breastfeeding, as the active substance, dantrolene, is excreted in human milk and undesirable effects on the breast-fed infant cannot be excluded, particularly during long-term therapy with Dantrium. If treatment of nursing mothers with Dantrium is required, breastfeeding must be discontinued.

Fertility
There is no data on the effects of dantrolene on fertility in humans.

4.7 Effects on ability to drive and use machines

During oral use of Dantrium, central nervous effects such as drowsiness or confusion can alter responsiveness to such an extent that the ability to drive actively or operate tools and machinery is reduced. This applies particularly at the start of treatment, when increasing the dose and in combination with alcohol or other medicinal products that depress the central nervous system.

4.8 Undesirable effects

Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse Drug Reactions
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon	Lymphocytic lymphoma
	Uncommon	Lymphoma
Blood and lymphatic system disorders	Uncommon	Aplastic anaemia
	Uncommon	Anaemia
	Uncommon	Leukopenia
	Uncommon	Thrombocytopenia
Immune system disorders	Uncommon	Hypersensitivity
	Uncommon	Anaphylactic reaction
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Common	Depression
	Common	Confusional state
	Common	Nervousness
	Uncommon	Hallucination
	Common	Insomnia
	Unknown	Disorientation
Nervous system disorders	Very common	Dizziness

	Very common	Somnolence
	Common	Headache[L]
	Common	Speech disorder[L]
	Common	Seizures
	Uncommon	Enhanced paresis in cases of amyotrophic lateral sclerosis or in the presence of bulbar paralytic symptoms
	Uncommon	Dysgeusia
	Unknown	Hypotonia
Eye disorders	Uncommon	Diplopia
	Uncommon	Lacrimation increased
	Common	Visual impairment
	Uncommon	Cardiac failure
	Uncommon	Tachycardia
	Common	Pericarditis
	Uncommon	Pleuropericarditis
	Unknown	Bradycardia
Vascular disorders	Uncommon	Phlebitis
	Uncommon	Blood pressure fluctuation
Respiratory, thoracic and mediastinal disorders	Common	Respiratory depression
	Common	Respiratory failure
	Very rare	Suffocation feeling
	Uncommon	Dyspnoea
Gastrointestinal disorders	Very Common	Diarrhoea
	Common	Abdominal cramps
	Common	Nausea
	Common	Vomiting
	Uncommon	Constipation (rarely progressing to signs of intestinal obstruction)
	Uncommon	Dysphagia
	Uncommon	Gastrointestinal haemorrhage
	Uncommon	Abdominal pain upper
	Uncommon	Salivary hypersecretion
	Unknown	Dyspepsia
	Unknown	Dry Mouth
Hepatobiliary disorders	Common	Hepatotoxicity/hepatitis
	Common	Jaundice
	Common	Cholestasis
Skin and subcutaneous tissue disorders	Common	Rash
	Common	Dermatitis acneiform/acne like rash/acne
	Uncommon	Hyperhidrosis
	Uncommon	Hair growth abnormal
	Uncommon	Pruritus
	Uncommon	Photosensitivity reaction

	Very rare	Urticaria
	Very rare	Eczema
Musculoskeletal and connective tissue disorder	Common	Muscular weakness
	Uncommon	Back pain
	Uncommon	Myalgia
Renal and urinary disorders	Uncommon	Urinary incontinence
	Uncommon	Pollakiuria
	Uncommon	Crystalluria
	Uncommon	Haematuria
	Uncommon	Urinary retention
	Unknown	Nocturia
	Very rare	Micturition disorder
	Unknown	Chromaturia
Reproductive system and breast disorders	Very rare	Erectile dysfunction
General disorders and administration site conditions	Very common	Fatigue
	Very common	Malaise
	Common	Chills
	Common	Pyrexia
	Very common	Asthenia
Investigations	Common	Liver function tests abnormal

In addition, the following specific undesirable effects have been noticed with the use of Dantrium Capsules:

- Precipitation of cerebral seizures, especially in children with cerebral palsy;
- pleuropericarditis and pericardial effusion, (accompanied by eosinophilia)
- pleural effusion (with associated eosinophilia),
- Diarrhoea (may be severe and may necessitate temporary withdrawal of dantrolene therapy).

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 are: muscular weakness, troubling hypotonia vision disorders (diplopia), changes in consciousness (lethargy, coma), fatigue, dizziness, vomiting, diarrhoea, tachycardia, hypo- or hypertension, pruritus, adverse hepatotoxic reactions.

In case of intoxication, if possible, gastric emptying should be performed and general measures for cardiac support and respiratory assistance should be planned. Dilution solution should be infused intravenously to avert the possibility of crystalluria.
The value of dialysis in dantrolene overdose is not known and there is no specific antidote for dantrolene overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: direct-acting muscle relaxants, ATC code: M03CA01.

Dantrolene decouples nerve stimulation and contraction in skeletal muscle probably by interfering with calcium release from the sarcoplasmic reticulum. Its action is selective and has no influence on neuromuscular transmission or any measurable effect on the excitable surface membrane.
Within the therapeutic dose range, smooth muscle and cardiac muscle are generally not affected by Dantrium. In vitro animal trials have indicated that effects on smooth muscle and heart muscle may occur at doses well above the therapeutic range; however, with conflicting results, so that no definitive statements can be made regarding such effects in humans.

5.2 Pharmacokinetic properties

Absorption:
The gastrointestinal absorption of dantrolene sodium is approximately 70% and leads to dose-dependent plasma concentrations. After administration of 25 mg dantrolene sodium 3.5•H2O, peak plasma concentrations were reached after 3-4 hours and were 0.22 µg/mL. The absolute bioavailability was 83.6% on average.

Distribution:
Dantrolene is reversibly bound to plasma albumin; as an in vitro binding constant, a value of 4.3×10^{-4} M^{-1} was established. For the transplacental passage of dantrolene, a factor of 0.4 was found.

Metabolism:
Metabolism in the liver takes place via 5-hydroxylation at the hydantoin ring, as well as via reduction of the nitro group to the amine with subsequent acetylation.
The parent substance and metabolites are mainly excreted via renal and biliary routes, with renal excretion occurring at a ratio of 79% 5-hydroxy dantrolene, 17% acetylamino-dantrolene and 1-4% unchanged dantrolene. The 5-hydroxy dantrolene metabolite is pharmacologically active, whilst acetylamino-dantrolene shows no muscle-relaxing effect.

Elimination:
Renal clearance (5-OH-dantrolene) is 1.8-7.8 L/h. The mean biological half-life in adults is 8.7 hours after an oral dose of 100 mg. In children with chronic spasticity, an elimination half-life of 7.3 h was found.

Duration and intensity of skeletal muscle relaxation in patients is dependent on blood levels.

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 128 mg/kg) and following oral administration the LD50 is around 3 g/kg in newborn rats (human equivalent dose 480 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 10.8 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. typhimurium test both in the presence 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 rats (at 20 mg/kg/day or above; human equivalent dose 3.2 mg/kg/day) and 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

Capsule fill:
Wheat starch
Talc
Magnesium Stearate
Lactose Monohydrate

Capsule shell:
Gelatin
Titanium Dioxide (E171)
Iron Oxide
Erythrosine (E127)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in blister packs, in the outer packaging, away from light and moisture.

6.5 Nature and contents of container

Polyvinyl chloride/aluminium blister packs of 100 capsules.

6.6 Special precautions for disposal and other handling.

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

PA 1336/004/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 19 March 2010.

10. DATE OF REVISION OF THE TEXT

29 March 2022