SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dantrium Capsules 25mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 25 mg dantrolene sodium.

Excipient with known effect: 161.0 mg of lactose monohydrate per capsule.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule

Dantrium Capsules 25 mg are presented as white/orange capsules of size 3.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dantrium Capsules are indicated for the treatment of chronic, severe spasticity of skeletal muscle in adults.

4.2 Posology and method of administration

Posology

Dosage for Use in Spasticity for Adults

For the individual patient the lowest dose compatible with optimal response is recommended. A recommended dosage increment scale is shown below:

1st week	One 25 mg capsule daily
2nd week	One 25 mg capsule twice daily
3rd week	Two 25 mg capsules twice daily

4th week	Two 25 mg capsules three times daily
5th week	Three 25 mg capsules three times daily
6th week	Three 25 mg capsules four times daily
7th week	One 100 mg capsule four times daily.

Each dosage level should be maintained for seven days in order to determine the patient's response. Therapy with a dose four times daily may offer maximum benefit to some patients. Maximum daily dose should not exceed 400 mg. In view of the potential for hepatotoxicity with long term use, if no observable benefit is derived from the administration of Dantrium after a total of 6-8 weeks, therapy should be discontinued.

Elderly

A similar dosage titration schedule should be used with the elderly.

Paediatric population

Dantrium is not recommended for use in children.

Method of administration

For oral use.

4.3 Contraindications

Dantrium is contraindicated where spasticity is utilised to sustain upright posture and balance in locomotion or whenever spasticity is utilised to obtain or maintain increased function. Dantrium is contraindicated in patients with evidence of hepatic dysfunction. Dantrium is not indicated for the treatment of acute skeletal muscle spasms.

Dantrium is contraindicated in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Hypersensitivity to the active substance or to any of the excipients listed in 6.1.

4.4 Special warnings and precautions for use

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

Patients should be instructed to contact their physician should signs or symptoms of hepatotoxicity (e.g., discoloured faeces, generalised pruritus, jaundice, anorexia, nausea, vomiting) occur during therapy.

Factors that may increase the risk of developing hepatotoxicity include:

- Higher daily doses (doses exceeding 400 mg daily)

- Duration of therapy (most frequently reported between 2 and 12 months of treatment)

- Female gender

- Age greater than 30 years

- Prior history of liver disease/dysfunction

- Receiving other hepatotoxic therapies concomitantly.

Spontaneous reports also suggest a higher proportion of hepatic events with fatal outcome in elderly patients.

At the start of Dantrium therapy, it is desirable to do liver function studies (SGOT/AST, SGPT/ALT, alkaline phosphatase, total bilirubin) for a baseline or to establish whether there is pre-existing liver disease. If baseline liver abnormalities exist and are confirmed, there is a clear possibility that the potential for Dantrium hepatotoxicity could be enhanced, although such a possibility has not yet been established.

Liver functions studies (e.g. serum, SGOT/AST, SGPT/ALT) should be performed at appropriate intervals during Dantrium therapy. If such studies reveal abnormal values, therapy should generally be discontinued. Only where benefits of the drug have been of major importance to the patient, should re-introduction or continuation of therapy be considered. Some patients have revealed a return to normal laboratory values in the face of continued therapy while others have not.

If symptoms compatible with hepatitis, accompanied by abnormalities in liver function tests or jaundice appear, Dantrium should be discontinued. If caused by Dantrium and detected early, the abnormalities in liver function have reverted to normal when the drug was discontinued.

Dantrium has been re-introduced in a few patients who have developed clinical signs, or elevated serum enzymes, of hepatocellular injury.

Re-introduction of Dantrium therapy should only be contemplated in patients who clearly need the drug, and only after complete reversal of the signs of hepatotoxicity and liver function tests. Patients being re-challenged with Dantrium should be hospital in-patients, and small, gradually increasing doses should be used. Laboratory test monitoring should be frequent, and the drug should be withdrawn immediately if there is any indication of recurrent liver abnormality. Some patients have reacted with unmistakable signs of liver abnormality upon administration of a challenge dose, whilst others have not.

The use of Dantrium with other potentially hepatotoxic drugs should be avoided.

There are isolated cases of possibly significant effects of Dantrium on the cardiovascular and respiratory systems. These cases also have other features

suggesting a pre-disposition to cardiovascular disease, and impaired respiratory function, particularly obstructive pulmonary disease. Dantrium should be used with caution in such patients.

Caution should be exercised in the simultaneous administration of tranquillising agents and alcohol.

This medicine contains lactose.

The colouring agent E110 can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.

4.5 Interaction with other medicinal products and other forms of interaction

Hyperkalaemia and myocardial depression have been observed in malignant hyperthermia-susceptible patients receiving intravenous dantrolene sodium and concomitant calcium channel blockers.

The effects of non-depolarizing muscle relaxants may be potentiated in patients administered Dantrium.

4.6 Fertility, pregnancy and lactation

Pregnancy

Although teratological studies in animals have proved satisfactory, Dantrolene sodium does cross the placenta and therefore the use of Dantrium is not advised during pregnancy.

Breast-feeding

Dantrolene sodium has been detected in human milk. Therefore, the use of Dantrium is not advised in nursing mothers.

Fertility

There is no data on the effects of Dantrium on human fertility.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive a motor vehicle or undertake potentially dangerous work until dantrium therapy has been stabilised, because some patients experience drowsiness and dizziness.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported unwanted effects associated with the use of Dantrium have been drowsiness, dizziness, weakness, general malaise, fatigue and diarrhoea. These effects are generally transient, occur early in treatment, and can often be obviated by careful determination and regulation of the dosage. Diarrhoea may be severe, and may necessitate temporary withdrawal of Dantrium. If diarrhoea recurs upon re-introduction of Dantrium, then Dantrium therapy should probably be withdrawn permanently.

Dantrium has a potential for hepatotoxicity. Symptomatic hepatitis (fatal and non-fatal) has been reported at various dose levels although the incidence is greater in patients taking more than 400 mg/day. Liver dysfunction as evidenced by blood chemical abnormalities alone (liver enzyme elevation) has been observed in patients exposed to Dantrium for varying periods of time.

Overt hepatitis has occurred at varying intervals after initiation of therapy, but has most frequently been observed between the second and twelfth month of treatment. The risk of hepatic injury appears to be greater in females, in patients over 30 years old and in patients taking concomitant medication. There is some evidence that hepatic injury is more likely in patients using concomitant oral oestrogen.

Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse Drug Reactions
Metabolism and nutrition disorders	Common	Anorexia
Psychiatric disorders	Common	Mental depression, mental confusion, insomnia, nervousness
Nervous system disorders	Common	Seizure, visual disturbances, speech disturbances, headache
Cardiac disorders	Common	Pericarditis
	Uncommon	Exacerbation of pre-existing cardiac insufficiency,
	Unknown	Bradycardia, tachycardia
Vascular disorders	Unknown	Labile blood pressure
Respiratory, thoracic and mediastinal disorders	Common	Pleural effusion with associated eosinophilia, respiratory depression
	Unknown	Dyspnoea
Gastrointestinal disorders	Common	Nausea and/or vomiting, abdominal pain
	Uncommon	Dysphagia, constipation (rarely progressing to signs of intestinal obstruction)
	Unknown	Gastrointestinal bleeding
Hepatobiliary disorders	Common	Hepatotoxicity (see section 4.4), liver function test disturbances

	Unknown	Jaundice, hepatitis
Skin and subcutaneous disorders	Common	Acne-like rash, skin rash
	Uncommon	Sweating
Renal and urinary disorders	Uncommon	Incontinence, increased urinary frequency, urinary retention, haematuria, crystalluria
General disorders and administration site conditions	Common	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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no known constellation of symptoms with acute overdose. Symptoms that may occur include, but are not limited to, muscular weakness, alterations in the state of consciousness (e.g. lethargy, coma), vomiting, and diarrhoea. For acute overdosage, general supportive measures and gastric lavage should be employed as well as measures to reduce the absorption of Dantrium. The theoretical possibility of crystalluria in overdose has not been reported for Dantrium, but would be treated according to general principles, including administration of fluids. The value of dialysis in dantrolene overdose is not known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

The receptor molecule for dantrolene sodium has not been identified. Radiolabelled dantrolene sodium binds to specific components of the striated muscle cell, namely the t-tubules and the sarcoplasmic reticulum; however the kinetics of binding varies between these two organelles. The binding of ryanodine is thought to compete with the binding of calcium in these organelles; further evidence for the specificity of binding is that dantrolene sodium inhibits the binding of the insecticide ryanodine to heavy sarcoplasmic reticulum vesicles from rabbit skeletal muscle. Under some conditions, dantrolene sodium will lower intra-sarcoplasmic calcium concentrations in the resting state. This may be more important in diseased muscle (e.g. in

malignant hyperthermia in humans and swine stress syndrome) than in muscle with normal function.

Dantrolene sodium does not bind to the same sites as calcium channel blocking drugs such as nitrendipine or calmodulin. There is no electrophysiological evidence that dantrolene sodium interferes with the influx of calcium from outside the cell. This may be one reason why paralysis by dantrolene sodium has never been reported in animals or man; the muscle cell has alternative sources of calcium which are not influenced by dantrolene sodium.

Pharmacodynamic effects

Whatever the molecular mechanism, the cardinal property of dantrolene sodium is that it lowers intracellular calcium concentration in skeletal muscle. Calcium concentrations may be lower in both the quiescent state, and as a result of a reduction in the release of calcium form the sarcoplasmic reticulum in response to a standard stimulus. This effect has been observed in striated muscle fibres from several species, and is not seen in myocardium. Fast fibres may be more sensitive than slow fibres to the action of dantrolene sodium.

Clinical efficacy and safety

Diverse other properties of dantrolene sodium have been observed in-vitro, and in animal studies. Dantrolene sodium may inhibit the release of calcium from the smooth endoplasmic reticulum of smooth muscle, but the significance of this observation is questionable; for example, dantrolene sodium has no effect on isolated human urinary bladder smooth muscle. Calcium dependent, pre-synaptic neurotransmitter release may also be inhibited by dantrolene sodium. Again, the clinical significance of this has not been demonstrated.

Studies on Isolated, Functional Muscle

Elevation of intracellular, free calcium ion concentration is an obligatory step in excitation-contraction coupling of skeletal muscle. Dantrolene sodium, therefore, acts as a muscle relaxant by a peripheral mechanism which is quite different, and easily distinguishable from neuromuscular junction blocking drugs. In contrast with compounds that relax skeletal muscle by acting principally on the central nervous system, dantrolene sodium acts directly on skeletal muscle cells. In rabbit atria, dantrolene sodium has no effect alone, but it may antagonise inotropic agents which act by increasing intramyocardial cell calcium e.g. the experimental drug anthopleurin-A.

5.2 Pharmacokinetic properties

Absorption

Dantrolene sodium is easily and almost completely absorbed from the gastrointestinal tract. After dosing on an empty stomach, plasma dantrolene sodium levels peak within three hours in most subjects.

Distribution

Dantrolene sodium is a highly lipophobic drug. In addition it lacks hydrophilicity. Dantrolene sodium binds to human serum albumin (HSA) with a molar ratio of 0.95 to 1.68 in-vitro. The association constant in-vitro is higher (2.3 to 5.4 x 10 -5 per mol). In-vitro dantrolene sodium can be displaced from HSA by warfarin, clofibrate and tolbutamide but these interactions have not been confirmed in humans (re. manufacturer's database). Single intravenous dose studies suggest that the primary volume of distribution is about 15 litres. Single oral doses achieve peak plasma concentration of about a quarter of that for a similarly sized intravenous dose.

Metabolism and Elimination

The biological half life in plasma in most human subjects is between 5 and 9 hours, although half lives as long as 12.1 □ 1.9 hours have been reported after a single intravenous dose. Inactivation is by hepatic metabolism in the first instance. There are two alternative pathways. Most of the drug is hydroxylated to 5-hydroxy-dantrolene. The minor pathway involves nitro-reduction to amino-dantrolene which is then acetylated (compound F-490). The 5-hydroxy metabolite is a muscle relaxant with nearly the same potency as the parent molecule, and may have a longer half life than the parent compound. Compound F-490 is much less potent and is probably inactive at the concentrations achieved in clinical samples. Metabolites are subsequently excreted in the urine in the ratio of 79 5-hydroxy-dantrolene: 17 compound F-490: 4 unaltered dantrolene (salt or free acid). The proportion of drug excreted in the faeces depends upon dose size.

5.3 Preclinical safety data

Carcinogenicity

Dantrolene sodium showed some evidence of tumourgenicity at high dose levels in Sprague-Dawley female rats. However, 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.

Sprague-Dawley female rats fed dantrolene sodium for 18 months at dosage levels of 15, 30 and 60 mg/kg/day showed an increased incidence of benign and malignant mammary tumours compared with concurrent controls. At the highest dose level, there was an increase in the incidence of benign hepatic lymphatic neoplasms. In a 30-month study at the same dose levels also in Sprague-Dawley rats, dantrolene sodium produced a decrease in the time of onset of mammary neoplasms. Female rats at the highest dose level showed an increased incidence of hepatic lymphangiomas and hepatic angiosarcomas.

The only drug-related effect seen in a 30-month study in Fischer-344 rats was a dose-related reduction in the time of onset of mammary and testicular tumours. A 24-month study in HaM/ICR mice revealed no evidence of carcinogenic activity.

The significance of carcinogenicity data relative to use of dantrolene sodium in humans is unknown.

Mutagenicity

Dantrolene sodium has produced positive results in the Ames S.Typhimurium bacterial mutagenesis assay in the presence and absence of a liver activating system.

Reproductive toxicity

Dantrolene sodium administered to male and female rats at dose levels up to 45 mg/kg/day showed no adverse effects on fertility or general reproductive performance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Maize starch,
Talc,
Magnesium stearate,
Lactose monohydrate

Capsule Shell
Gelatine
Titanium dioxide (E171)
Sunset yellow (E110)

6.2 Incompatibilities

None.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Dantrium capsules are supplied in high density polyethylene (HDPE) bottles with HDPE caps. One bottle contains 100 capsules.

6.6 Special precautions for disposal

A patient leaflet is provided for details of use and handling of the product.

7 MARKETING AUTHORISATION HOLDER

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