NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DANTRIUM® Capsule, 25 mg

DANTRIUM® Capsule, 50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DANTRIUM Capsule 25 mg contains 25 mg dantrolene sodium hemiheptahydrate
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Dantrolene sodium is1-{[5-(p-nitrophenyl) furfurylidene]amino} hydantoin sodium hydrate. The anhydrous salt has a molecular weight of 336. The hydrated salt contains approximately 15% water (3 1/2 moles) and has a molecular weight of 399.

Excipient(s) with known effect

- Lactose monohydrate
- Sodium lauril sulfate
- Sunset yellow FCF.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

It is an orange powder, slightly soluble in water, but due to its slightly acidic nature the solubility increases somewhat in alkaline solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DANTRIUM is indicated in controlling the manifestations of clinical spasticity resulting from serious chronic disorders such as spinal cord injury, stroke, cerebral palsy, or multiple sclerosis. It is of particular benefit to the patient whose functional rehabilitation has been retarded by the sequelae of spasticity. Such patients must have presumably reversible spasticity where relief of spasticity will aid in restoring residual function. There is no evidence that patients with contractures will benefit. DANTRIUM is not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders or electroconvulsive therapy.

If improvement occurs, it will ordinarily occur within the dosage titration schedule (see section 4.2), as manifested by a decrease in the severity of spasticity and the ability to resume a daily function not quite attainable without DANTRIUM.

Occasionally, subtle but meaningful improvements in spasticity may occur with DANTRIUM therapy. In such instances information regarding improvement should be solicited from the patient directly and from those who are in constant daily contact and attendance with the patient. Brief withdrawal of DANTRIUM for a period of 2 to 4 days will frequently demonstrate exacerbation of the manifestation of spasticity and may serve to confirm a clinical impression.

A decision to continue the administration of DANTRIUM on a long term basis is justified if introduction of the drug into the patient's regimen produces a significant reduction in painful and/or disabling spasticity such as clonus, or permits a significant reduction in the intensity and/or degree of nursing care required, or rids the patient of an annoying manifestation of spasticity considered important by the patient themselves.

4.2 Dose and method of administration

Dose

Prior to the administration of DANTRIUM consideration should be given to the potential response to treatment. A decrease in spasticity sufficient to allow a daily function not otherwise attainable should be the therapeutic goal of treatment with DANTRIUM. Refer to section 4.1 for a description of the response to be anticipated.

It is important to establish a therapeutic goal (regain and maintain a specific function such as therapeutic exercise program, utilisation of braces, transfer manoeuvres, etc.) before beginning DANTRIUM therapy. Dosage should be increased until the maximum performance compatible with the dysfunction due to underlying disease is achieved. No further increase in dosage is then indicated.

Usual dosage

It is important that the dosage be titrated and individualised for maximum effect. The lowest dose compatible with optimal response is recommended.

In view of the potential for liver damage in long-term DANTRIUM use, therapy should be stopped if benefits are not evident within 45 days.

Adults

Begin therapy with 25 mg once daily; increase to 25 mg two, three, or four times daily and then by increments of 25 mg up to as high as 50 mg two, three or four times daily if necessary. The maximum recommended dose is 200 mg/day. As most patients will respond to this or a lower dose, and hepatotoxicity appears to be dose-related above 200 mg/day, higher doses should be used only rarely and with close monitoring (see section 4.4). Doses higher than 400 mg/day should not be used.

Each dosage level should be maintained for four to seven days to determine the patient's response. The dose should not be increased beyond, and may even have to be reduced to, the amount at which the patient received maximal benefit without adverse effects.

Special populations

Paediatric population

A similar approach should be utilised starting with 0.5 mg/kg of body weight twice daily; this is increased to 0.5 mg/kg three or four times daily and then by increments to a maximum of 2 mg/kg three times a day. Doses higher than 50 mg four times daily should not be used in children.

4.3 Contraindications

Active hepatic disease, such as acute hepatitis and active cirrhosis, is a contraindication for use of DANTRIUM. 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.

4.4 Special warnings and precautions for use

If no observable benefit is derived from the administration of DANTRIUM after a total of 45 days, therapy should be discontinued. The lowest possible effective dose for the individual patient should be prescribed.

Hepatotoxicity

DANTRIUM should be used with caution in patients with a history of previous liver disease or dysfunction.

It is important to recognise that DANTRIUM 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. Hepatotoxicity appears to be dose-related above 200 mg/day and this is the maximum recommended dose. Patients receiving higher doses should be closely monitored. Even sporadic short courses of doses above 400 mg/day 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 DANTRIUM 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. At the start of DANTRIUM therapy, it is essential to do liver function studies (SGOT, SGPT, 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.

DANTRIUM should be used only in conjunction with appropriate monitoring of hepatic function. Liver function studies (e.g. SGOT or SGPT) 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 reinitiation 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 characteristically have reverted to normal when the drug was discontinued. DANTRIUM therapy has been reinstituted in a few patients who have developed clinical and/or laboratory evidence of hepatocellular injury. If such reinstitution of therapy is done, it should be attempted only in patients who clearly need DANTRIUM and only after previous symptoms and laboratory abnormalities have cleared. The patient should be hospitalised and the drug should be restarted in very small and gradually increasing doses. Laboratory monitoring should be frequent and the drug should be withdrawn immediately if there is any indication of recurrent liver involvement. Some patients have reacted with unmistakable signs of liver abnormality upon administration of a challenge dose, while others have not.

DANTRIUM should be used with particular caution in females and in patients over 35 years of age in view of the apparently greater likelihood of drug-induced, potentially fatal, hepatocellular disease in these groups. Careful consideration should be given to the possible risks involved in the concurrent use of hormonal oral contraceptives with DANTRIUM (see section 4.5).

Renal Impairment

In patients with impaired renal function, dosage may have to be significantly reduced and the possibility of a drug related further impairment borne in mind (see section 4.8).

Pulmonary Impairment

DANTRIUM should be used with caution in patients with impaired pulmonary function, particularly those with obstructive pulmonary disease, and in patients with severely impaired cardiac function due to myocardial disease. DANTRIUM is associated with pleural effusion with associated eosinophilia.

Photosensitivity

DANTRIUM might possibly evoke a photosensitivity reaction; patients should be cautioned about exposure to sunlight while on therapy.

Neuroleptic Malignant Syndrome

The published literature has included some reports of DANTRIUM use in patients with Neuroleptic Malignant Syndrome (NMS). DANTRIUM capsules are not indicated for the treatment of NMS and patients may expire despite treatment with DANTRIUM capsules.

Use in the Elderly

Spontaneous reports suggest a higher proportion of hepatic events with fatal outcome in elderly patients receiving DANTRIUM. In general dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. As with all patients receiving DANTRIUM, it is recommended that elderly patients receive the lowest dose compatible with the optimal response (see section 4.2).

Long-term Safety

Long-term safety of DANTRIUM in humans has not been established. Chronic studies in rats, dogs and monkeys at dosages greater than 30 mg/kg/day showed growth or weight depression and signs of hepatopathy and possible occlusion nephropathy, all of which were reversible upon cessation of treatment. 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 and, at the highest dosage an increase in the incidence of hepatic lymphangiomas and hepatic angiosarcomas. These effects were not seen in 2 1/2-year studies in Sprague-Dawley or Fischer 344 rats or in 2-year studies in mice of the HaM/ICR strain.

Paediatric population

The long-term safety of DANTRIUM in children under the age of 5 years has not been established. Because of the possibility that adverse effects of the drug could become apparent only after many years, a benefit-risk consideration of the long-term use of DANTRIUM is particularly important in paediatric patients.

4.5 Interaction with other medicines and other forms of interaction

While a definite drug interaction with oestrogen therapy has not yet been established, caution should be observed if the two drugs are to be given concomitantly. Hepatotoxicity has occurred more often in women over 35 years of age receiving concomitant oestrogen therapy.

There are very rare reports of cardiovascular collapse in patients treated simultaneously with verapamil and dantrolene sodium. The combination of therapeutic doses of intravenous dantrolene sodium and verapamil in halothane/α-chloralose anaesthetised swine has resulted in ventricular fibrillation and cardiovascular collapse in association with marked hyperkalaemia. Until the relevance of these findings to humans is established, the combination of dantrolene sodium and calcium channel blockers, such as verapamil, is not recommended.

The effects of non-depolarising muscle relaxants may be potentiated in patients administered dantrolene.

Administration of DANTRIUM may potentiate vecuronium-induced neuromuscular block.

Dantrolene causes dizziness, drowsiness, and weakness; alcohol and other CNS depressants such as sedatives and tranquilising agents may intensify this effect.

4.6 Fertility, pregnancy and lactation

Fertility

No data available.

Pregnancy - Category B2

The safety of DANTRIUM for use in women who are or who may become pregnant has not been established; hence it should be given only when the potential benefits have been weighed against possible hazard to mother and child. Dantrolene crosses the placenta.

Lactation

DANTRIUM should not be used by nursing mothers. Dantrolene has been detected in human breast milk.

4.7 Effects on ability to drive and use machinery

Patients should be cautioned against driving a motor vehicle or participating in hazardous occupations while taking DANTRIUM. Dantrolene causes dizziness, drowsiness and weakness; alcohol and other CNS depressants may intensify this effect.

4.8 Undesirable effects

The most frequently occurring adverse effects of DANTRIUM have been drowsiness, dizziness, weakness, general malaise, fatigue, and diarrhoea. These effects have been experienced by approximately 20% of patients. They are generally transient, occurring early in treatment, and can often be obviated by beginning with a low dose and increasing dosage gradually until an optimal regimen is established. Diarrhoea may be severe and may necessitate temporary withdrawal of DANTRIUM therapy. If diarrhoea recurs upon readministration of DANTRIUM, therapy should probably be withdrawn permanently.

Other less frequent adverse effects, listed according to system, are:

Gastrointestinal	Constipation, rarely progressing to signs of intestinal obstruction, GI bleeding, anorexia, gastric irritation, abdominal cramps, vomiting, nausea, dry mouth, saliva hypertension, dyspepsia, dysphagia.
Haematologic	Aplastic anaemia, anaemia, leukopenia, lymphocytic lymphoma, thrombocytopenia.
Hepatobiliary	Liver function test disturbances, hepatitis (see section 4.4).
Neurologic	Speech disturbance, seizure, headache, light-headedness, visual disturbance, diplopia, alteration of taste.
Cardiovascular	Tachycardia, erratic blood pressure, heart failure, phlebitis, exacerbation of cardiac insufficiency.
Psychiatric	Mental depression, mental confusion, increased nervousness, insomnia.
Urogenital	Increased urinary frequency, crystalluria, haematuria, difficult erection, urinary incontinence and/or nocturia, difficult urination, chromaturia and/or urinary retention. A transient lowering of G.F.R. and renal plasma flow after 8 weeks' therapy has been reported.
Integumentary	Abnormal hair growth, acne-like rash, pruritus, urticaria, eczematoid eruption, sweating.

Musculoskeletal	Myalgia, backache.
Respiratory	Feeling of suffocation, respiratory depression, respiratory failure.
Special Senses	Excessive tearing.
Hypersensitivity	Pleural effusion with associated eosinophilia, pericarditis, anaphylaxis.
Other	Chills and fever.

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

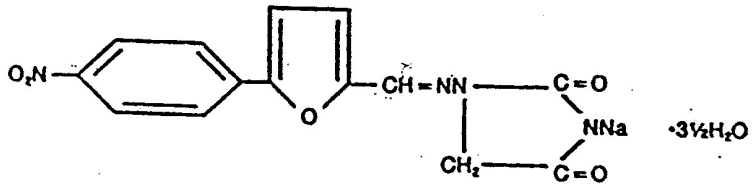
Signs and symptoms are likely to be an extension of those under **ADVERSE EFFECTS**. Unconsciousness may supervene. Total skeletal paralysis is unlikely in conscious patients. For acute overdosage general supportive measures should be employed. Intravenous fluids should be administered in fairly large 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. To date, no experience has been reported with dialysis; its value in DANTRIUM overdosage is not known.

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

The structural formula for the hydrated salt is:



Mechanism of action and pharmacodynamic effects

In isolated nerve-muscle preparations, DANTRIUM has been shown to produce relaxation of the contractile state of the skeletal muscle by an effect beyond the myoneural junction and directly on the muscle itself. In these preparations DANTRIUM uncouples the excitation and

contraction of the skeletal muscle, probably by interfering with the release of calcium ions from the sarcoplasmic reticulum. This effect appears to be more pronounced in fast muscle fibres as compared to slow ones, but generally affects both. A central nervous system effect occurs with drowsiness, dizziness and generalised weakness in some 20% of cases. The extent of the involvement of the CNS in DANTRIUM-induced muscle relaxation is unknown.

5.2 Pharmacokinetic properties

Absorption

The absorption of DANTRIUM after oral administration in humans is incomplete and slow, but consistent and dose related blood levels are obtained. The duration and intensity of skeletal muscle relaxation is related to the dosage and blood levels.

Distribution

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.

Biotransformation and Elimination

The mean biological half-life of DANTRIUM in adults is 8.7 hours after a 100 mg dose. Specific metabolic pathways in the degradation and elimination of DANTRIUM in human subjects have been established. Metabolic patterns are similar in adults and children. In addition to the parent compound, dantrolene, which is found in measurable amounts in blood and urine, the major metabolites noted in body fluids are the 5-hydroxy analogue and the acetamido analogue.

Since DANTRIUM is probably metabolised by hepatic microsomal enzymes, enhancement of its metabolism by other drugs is possible. However, neither phenobarbital nor diazepam appears to affect DANTRIUM metabolism.

Approximately 20 to 25% of an oral dose appears in the urine in the metabolised form and 1% or less is excreted unchanged. About 45 to 50% of the same oral dose appears in the bile.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

Carcinogenicity in humans cannot be fully excluded, so this possible risk of chronic administration must be weighed against the benefits of the drug (i.e. after a brief trial) for the individual patient.

Reproductive and developmental toxicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Ink
Iron oxide red
Iron oxide yellow
Lactose monohydrate
Magnesium stearate
Maize starch
Purified talc
Sodium lauril sulfate
Sunset yellow FCF
Titanium dioxide.

6.2 Incompatibilities

No data available.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

DANTRIUM capsules are available as:

25 mg capsules: Orange and tan, opaque, coded "DANTRIUM 25 mg", "0149" and "0030" with a single line all in black.

50 mg capsules: Orange and tan, opaque, coded "DANTRIUM 50 mg", "0149" and "0031" with a double line all in black.

DANTRIUM capsules are available in plastic bottles of 100.

Note: DANTRIUM is available for the continuing management of patients whose treatment was initiated in a hospital or other institution recognised as a special centre for rehabilitation.

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
PO Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

07 September 2006

10. DATE OF REVISION OF THE TEXT

4 February 2019

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformat to MedSafe Data Sheet guidance