PRODUCT MONOGRAPH

PrDANTRIUM® Capsules

dantrolene sodium capsules, Mfr. Std.

25 mg & 100 mg

Skeletal Muscle Relaxant

Par Pharmaceutical Companies
Parsippany, NJ 07054, USA

Date of Preparation:
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Distributed by: Methapharm Inc.
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Table of Contents

PRODUCT MONOGRAPH

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	capsules 25 mg and 100 mg	lactose *For a complete listing see Dosage Forms, Composition and Packaging Section*

INDICATIONS AND CLINICAL USE

Dantrium is indicated for:

- Controlling the manifestations of a chronic spasticity of skeletal muscle resulting from such conditions as spinal cord injury, cerebral palsy, multiple sclerosis, and stroke, whenever such spasticity results in a decrease in functional use of residual motor activity.
- The pre-operative management of malignant hyperthermia-susceptible surgical patients.
- The post-crisis follow-up management of patients stabilized with the intravenous product (for information regarding the intravenous product see the Dosage and Administration Section of the Dantrium Intravenous Product Monograph).

Dantrium is not indicated in the relief of skeletal muscle spasms due to rheumatic disorders.

CONTRAINDICATIONS

Dantrium is contraindicated in:

- Patients with known hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Cases where spasticity is needed to maintain function. Skeletal muscle spasticity without suitable volitional activity (residual motor activity) may be of value in rehabilitation programs aimed toward sustaining upright posture and balance, and may assist a patient's locomotor pattern. Relief of such spasticity would reduce rather than increase function.
- Patients with compromised pulmonary function, particularly those with obstructive pulmonary disease.

- Patients with active hepatic disease, such as hepatitis and cirrhosis.

WARNINGS AND PRECAUTIONS

Serious Warning and Precautions

Hepatotoxicity
Dantrium (dantrolene sodium) has a potential for hepatotoxicity and symptomatic hepatitis, and should not be used in conditions other than those recommended. Risk of hepatic injury appears to be greater in female patients, in patients over 30 years of age, in patients taking other medication(s), and in patients receiving other hepatotoxic therapies concomitantly. Dantrium may exacerbate pre-existing liver dysfunction. Dantrium should not be used without appropriate evaluation and monitoring of hepatic function before and throughout treatment, including frequent determinations of alanine transferase (ALT) and aspartate transferase (AST) in blood serum. A trial administration of Dantrium is recommended and if after 45 days no observable benefit is evident, Dantrium should be discontinued. The lowest possible effective dose for the individual patient should be prescribed.

Carcinogenicity

There is evidence of low-grade carcinogenicity activity of Dantrium in rats. Thus, potential carcinogenicity in humans cannot be disregarded (see **Carcinogenesis and Mutagenesis**)

Cardiovascular
Dantrium should be used with caution in patients with impaired myocardial function.

Carcinogenesis and Mutagenesis
Toxicity studies in animals provided evidence of low-grade carcinogenic activity of Dantrium in the rat (see **Part II, TOXICOLOGY**). In view of the animal findings, potential carcinogenicity in humans cannot be disregarded. Therefore, the potential benefits of the drug should be weighed against the possible risks of drug use for the individual patient. Consideration should be given as to whether the patient has responded to other medication and to benefits of the trial administration of Dantrium as recommended above (see **Serious Warnings and Precautions**, **Hepatotoxicity**). In assessing risk acceptability, the age of the patient, the degree of disability and life expectancy should also be considered. The long term safety of Dantrium has not yet been established.

Driving and Operating Machinery
Dantrolene causes dizziness, drowsiness, and weakness; alcohol and other central nervous system (CNS) medications may intensify this effect. Patients should be instructed not to drive a

motor vehicle or engage in activities requiring unimpaired judgement and coordination during the first week of Dantrium therapy.

Hepatic / Biliary / Pancreatic

Fatal and non-fatal hepatitis have occurred at various dosage levels. The incidences reported in patients taking up to 400 mg per day are much lower than in those taking doses of 800 mg or more per day. Even sporadic short courses of the higher dosage levels markedly increased the risk of serious hepatic injury. Overt hepatitis has been observed most frequently after the second month of therapy. Spontaneous reports also suggest a higher proportion of hepatic events with fatal outcome in elderly patients.

Liver dysfunction, as evidenced by elevated concentrations of liver enzymes in blood serum, has been observed in a number of patients receiving Dantrium for less than 60 days.

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

See **Serious Warnings and Precautions**.

Musculoskeletal

Although subjective weakness attributable to Dantrium is usually transient, some patients feel excessively weak as long as Dantrium therapy is continued. Such patients may not be able to manipulate rehabilitation devices such as wheelchairs, crutches, braces, walkers, or canes. Careful attention should be given to patients utilizing these devices. Dantrium should be discontinued if the weakness persists and interferes with the use of a rehabilitation device.

Respiratory

Dantrium should be used with caution in patients with impaired pulmonary function.

Sensitivity

The possibility of cross-sensitivity with compounds of related chemical structure exists; however, no such reactions were reported in extensive clinical trials.

Skin

Although photosensitization has not been a problem in clinical trials of Dantrium, it is possible that in some subjects the drug might evoke a phototoxic response.

Special Populations

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

Nursing Women: Dantrium should not be used in nursing mothers. Dantrolene has been detected in human milk.

Paediatrics: In view of the **Serious Warnings and Precautions**, it is particularly important to assess risk acceptability before Dantrium is used in paediatric patients. Since there is insufficient experience with the use of Dantrium in young children (under 5 years of age), the drug is usually not recommended in this age group.

Monitoring and Laboratory Tests

Liver function tests should be performed before therapy and during therapy at adequate intervals. (See **Serious Warnings and Precautions**.)

In addition, in long-term therapy, periodic clinical and laboratory evaluation of organ systems, including haematopoietic, and renal studies, should be performed.

ADVERSE REACTIONS

Side effects most frequently reported were drowsiness, weakness, dizziness, malaise, fatigue and diarrhoea. These effects were generally transient and may be avoided with initial low doses and a gradual increase to optimal doses. Diarrhoea may be of sufficient severity to warrant temporary or possibly permanent withdrawal of medication.

Less commonly reported effects are listed by systems:

Cardiovascular: Tachycardia and erratic blood pressures, phlebitis, exacerbation of cardiac insufficiency.

Gastrointestinal: Constipation, rarely progressing to signs of intestinal obstruction, abdominal pain, anorexia, gastric irritation and bleeding, abdominal cramps, swallowing difficulty, and nausea with or without vomiting.

Hepatobiliary: Liver function test disturbances, hepatotoxicity, and liver failure (see **Warnings and Precautions**).

Respiratory: Respiratory depression.

CNS: Speech and visual disturbances, seizure, headache, lightheadedness, taste alterations, mental depression, confusion, nervousness, diplopia and insomnia.

Urogenital: Increased urinary frequency, crystalluria, difficult erection, urinary incontinence and/or nocturia, difficult urination and/or urinary retention.

Musculoskeletal: Myalgia, backache.

Integumentary: Acne-like rash, pruritus, urticaria, eczematoid eruption, abnormal hair growth, sweating, skin eruptions.

Hypersensitivity: Pleural effusion with pericarditis or with associated eosinophilia.

Other: Chills, fever, excessive tearing, feeling of suffocation.

Abnormal Hematologic and Clinical Chemistry Findings

Alterations of liver function studies tests attributable to Dantrium have been observed. It is therefore advisable to perform liver function tests before and during therapy (see **Warnings and Precautions**).

DRUG INTERACTIONS

Drug-Drug Interactions

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

Although the primary pharmacologic effect of Dantrium is exerted directly on skeletal muscle, an apparent transient CNS effect also may exist. Therefore, caution should be exercised in the concomitant administration of tranquilizing agents.

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

Drug-Herb Interactions

Interactions with herbs have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- It is important that the dosage be titrated and individualized for maximum optimal effect. The lowest dose compatible with optimal response is recommended. In view of the potential for liver damage during long-term use, therapy with Dantrium should be discontinued if benefits are not evident within 45 days. (See **Serious Warnings and Precautions**).

- 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. See ACTION AND CLINICAL PHARMACOLOGY for description of possible areas of response.

- It is important to establish a **therapeutic goal** (regain and maintain a specific function such as therapeutic exercise program, utilization 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.

Recommended Dose and Dosage Adjustment

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, to 100 mg two, three, or four times daily, if necessary. As most patients will respond to a dose of 400 mg/day or less, rarely should doses higher than 400 mg/day be used. Each dosage level should be maintained for four to seven days, depending on the patient's tolerance, and should be increased only if the therapeutic goal has not been attained.

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.

Children: A similar approach should be utilized 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 of 0.5 mg/kg up to as high as 3.0 mg/kg two, three, or four times daily, if necessary. Doses higher than 100 mg four times daily should not be used in children. (See **WARNINGS AND PRECAUTIONS**, **Special Population**, **Paediatrics**.)

Missed Dose

Patients should be instructed that if they miss a dose of Dantrium, they should take it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Patients should not take two doses at once.

OVERDOSAGE

Symptoms and Signs

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 diarrhea.

A single case has been reported of a patient with an 18-year history of multiple sclerosis who consumed 1600 mg of Dantrium per day for 13 days (a total of 20,800 mg). Other than feeling slightly weaker and "rubbery," the patient appeared to suffer no clinical manifestations of overdosage. Liver function values were transiently elevated although the patient did not become jaundiced.

Recommended management

For acute overdosage general supportive measures should be employed, along with immediate gastric lavage. 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 made available. Electrocardiographic monitoring should be instituted, and the patient carefully observed. No experience has been reported with dialysis, hence its value in Dantrium overdosage is not known.

ACTION AND CLINICAL PHARMACOLOGY

Recordings of muscle tensions and electrical activity in both animal and man suggest that Dantrium (dantrolene sodium) has a direct inhibitory effect on the development of contractile tension. Spastic patients receiving Dantrium have shown a 40 - 70% reduction in the skeletal muscle tension induced by direct electrical stimulation of the motor nerve with no alteration of the electromyogram (EMG). This decrease in contractile tension can be attributed to an effect of Dantrium beyond the myoneural junction. Total paralysis does not occur since the Dantrium-induced change in the contractile state of skeletal muscle is limited in magnitude. The reduction in contractile activity accounts for the ability of Dantrium to diminish spasticity resulting from pathological states associated with a hyperactive stretch reflex.

Dantrium also produces central nervous system effects resulting in such manifestations as drowsiness, dizziness and generalized weakness.

Pharmacokinetics

Absorption of Dantrium is slow; dose-related blood levels are obtained which peak in 4 to 6 hours after a single oral dose. The peak pharmacologic effect generally occurs in 1½ to 3 hours at concentrations of 50 to 75 percent of the peak plasma level. 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. Metabolism is rapid via hepatic microsomal enzymes. The major metabolites in humans are a 5-hydroxy analog and an acetamino analog. Urinary excretion of Dantrolene and metabolites occurs in an initially rapid phase (t-½, 2.5 to 3 hours) followed by a slower phase over a 24 hour period. Dantrium is also removed by biliary excretion.

STORAGE AND STABILITY

Store at room temperature (15°C – 30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dantrium is available in opaque orange and brown capsules of 25 mg (opaque orange cap and opaque light tan to brown body) coded with 1 black bar and DANTRIUM 25 mg 0149 0030, bottles of 100, and opaque orange and brown capsules of 100 mg (opaque orange cap and opaque light tan to brown body) coded with 3 black bars and DANTRIUM 100 mg 0149 0033, bottles of 100.

Each capsule contains the following inactive ingredients: edible black ink, gelatin, lactose, magnesium stearate, starch, talc, titanium dioxide, iron oxide red, iron oxide yellow.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

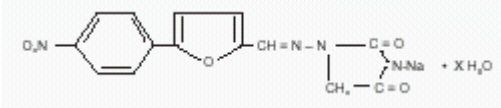
Proper name: dantrolene sodium

Chemical name: 1-[5-(p-nitrophenyl)-furfurylidene] amino hydantoin sodium hydrate

Molecular formula: $C_{14}H_9N_4NaO_5 \cdot 3½ H_2O$

Molecular mass: 399.29 (hydrous)
336.23 (anhydrous)

Structural formula:



Physical properties: orange powder, slightly soluble in water, but due to its slightly acidic nature the solubility increases somewhat in alkaline solution.

CLINICAL TRIALS

Dantrium has been studied in the treatment of selected patients with moderate to severe skeletal muscle spasticity resulting from stroke, spinal cord injury, cerebral palsy, multiple sclerosis, and other neuropathies. It seems to act directly on the skeletal muscle and has been found useful whenever manifestations of spasticity such as increased muscular resistance to stretch, clonus, and exaggerated reflex posturing interfere with therapeutic exercise programs, utilization of braces, transfer manoeuvres, posture equilibrium, ambulation, and activities of daily living.

Marked reduction or even cessation of spontaneous involuntary movements was observed in many patients receiving Dantrium. The extent to which Dantrium may contribute toward improvement in spasticity and activities in daily living can be tested by withdrawing the drug for 2 to 4 days and observing whether an exacerbation of the patient's condition occurs.

DETAILED PHARMACOLOGY

Dantrium causes marked, dose-dependent skeletal muscle relaxation in laboratory animals with a long duration of action. The pharmacologic profile of Dantrium in animals is unlike neuromuscular blocking agents in that total muscle paralysis and/or respiratory depression do not occur.

There is a wider margin between doses causing muscle relaxation and doses causing motor incoordination with Dantrium than with centrally acting muscle relaxants. Skeletal muscle relaxation is not associated with anaesthetic or analgesic action. Impairment of cornea or pinna reflexes has not been observed in animals treated with Dantrium.

Various studies both **in vivo** and **in vitro** demonstrated the apparent selectivity of action of Dantrium for skeletal muscle. There were some non-specific depressant effects seen in several smooth muscle studies and insignificant effects in cardiac muscle in doses which cause skeletal muscle relaxation. Nerve transmission was not affected by Dantrium in several animal studies.

It has been shown that Dantrium has no effect on the propagated action potential recorded on the muscle membrane, and the total membrane capacitance is not decreased by the drug, indicating that it does not disrupt the function of the transverse tubular system, and acts at a point beyond the electrically excitable surface membrane. Evidence obtained **in vitro** with muscle preparations exposed to caffeine, an agent known to cause muscle contractions by releasing internal Ca^{++} stores in muscle, suggests that Dantrium acts on skeletal muscle by altering the Ca^{++} release mechanisms. Such an action could explain the apparent specificity of Dantrium for skeletal muscle.

Animal studies have indicated that Dantrium is metabolized by hydrolysis, hydroxylation, nitro-reduction and acetylation of the resulting amine.

Four corresponding metabolites have been identified which probably do not contribute significantly to the activity of Dantrium. Maximal blood levels following oral administration are reached in approximately 1 hour. In dogs approximately 40% of an i.v. dose of Dantrium is excreted as the hydroxylated metabolite in bile whereas only 1% of the dose is excreted in this manner by the rat. High biliary concentrations of this metabolite have also been found in the Rhesus monkey. Total excretion of known metabolites in the urine is estimated at approximately 3% in the dog and approximately 10% in the rat.

TOXICOLOGY

The oral LD_{50} of dantrolene sodium in newborn Sprague-Dawley rats was 2902 mg/kg. No young adult rats were killed with doses up to 18,000 mg/kg. Pertinent clinical signs were inactivity, lethargy, weakness, gasping, diarrhoea, yellowing of skin colour, decreased growth rate or weight loss, and death. Tubular degeneration and necrosis, cortical abscesses and pelvic necrosis occurred in kidneys. No deaths occurred within 48 hours in adult rabbits and mice, with oral doses up to 8 or 9 g/kg, respectively. Crystals were observed in the urinary and the gallbladders of rabbits.

Three subacute toxicity studies were conducted in rats with oral doses up to 500 mg of dantrolene sodium/kg for 28 days and up to 86 mg/kg for 88 days. Body weight gains were reduced significantly by doses of 43.8 mg/kg. Relative kidney and liver weights were increased by doses of 15.5 mg/kg and absolute liver weights by 86 mg/kg for 88 days. Increased serum

alkaline phosphatase and AST occurred with doses of 62.5 mg/kg. Rats dosed with 500 mg/kg for 28 days had increased serum alkaline phosphatase, AST, fasting plasma glucose, plasma urea nitrogen, serum creatinine, and decreased urine specific gravity. Renal tubules were plugged by drug crystals, and tubular dilatation, degeneration, necrosis and hematuria resulted.

Chronic toxicity studies were conducted in Beagle dogs for 1 year. Oral doses of 15 mg/kg/day produced no detectable effects. At 30 mg/kg/day, there was a suppression of weight gain and sporadic increases in bromosulphalein (BSP) retention. A regimen of increasing doses (90 mg/kg for the first 206 days followed by 180 mg/kg for 14 days and 360 mg/kg for an additional 82 days) caused marked loss in body weight, increased AST activity and BSP retention, normocytic orthochromic anaemia, urinary anisotropic crystals and, in one dog necropsied at day 270, intrahepatic cholestasis. Recovery occurred after discontinuation of drug administration.

A one-year oral toxicity study also was conducted with Rhesus monkeys. Initial doses of 0, 15, 30, and 60 mg/kg were used. Because of the lack of clinical toxicity during the first 6 months, the dosage levels were doubled at the end of the first 6 months. At 9 months the dosage level for the high dose group was again doubled and these animals were then maintained on 240 mg/kg/day until the termination of the study. A dose-dependent lowering of body weight gain was observed at 12 months. Urinary crystals were noted in one animal at the middle (60 mg/kg/day) dosage level at 11½ to 12 months. Urinalysis at 6 and 12 months also indicated drug-related increase in blood elements. During the last 6 months, a generally lower albumin/globulin ratio at all dosage levels, a slight, apparently dose-related cholesterol-lowering effect, a higher serum alkaline phosphatase, a high AST level in the two high dosage levels, and relatively lower serum creatinine levels in the high dosage groups were noted. Chronic hepatic cholangitis was observed at necropsy in some mid and high dosage level animals.

Dantrolene sodium was administered in the diet to mature Sprague-Dawley rats for 18 months at levels of 15, 30, and 60 mg/kg daily. Treated rats showed a lower body weight gain compared to controls and damage to the liver. There was an increase in the incidence of mammary adenofibromas in the females. Other drug-related changes (seen only at the 30 and 60 mg/kg daily dosage levels) were increased incidences of bile duct cystadenomas, and increased signs of malignancy in mammary tumours in females. At the 60 mg/kg daily level the number of metastasizing mammary adenocarcinomas in female rats was increased significantly; anisotropic urinary crystals were found in both male and female groups.

Because of these findings, lifetime tumorigenesis studies were conducted in Sprague-Dawley and Fischer 344 rats. The treated Sprague-Dawley rats received dantrolene sodium in the diet at levels of 15, 30, and 60 mg/kg daily for 18 months and the Fischer 344 rats received the same levels for 20 months. The animals subsequently were maintained on a standard diet until 90% of each treatment group died spontaneously. Dantrium produced in the female Sprague-Dawley rats a linear, dose-related increase in the number of rats with malignant neoplasms, and a decrease in the time of onset of mammary neoplasms. There were also increased incidence of benign hepatic tumours including lymphangiomas and bile duct cystadenomas, and angiosarcomas. In Fischer rats, there was a significant, dose-related reduction in the times of onset of mammary and testicular tumours.

A two year tumorigenesis study was conducted in Swiss mice (CD$^{(R)}$ - 1 HaM/ICR). Dantrolene sodium was fed to mice at levels of 15, 30, and 60 mg/kg/day for 15 months and then the mice were maintained on a standard diet for 9 additional months. There was an increased incidence of benign angiomatous neoplasms.

Effects on Reproduction: Dietary doses of 0, 15, or 45 mg/kg of dantrolene sodium were given to rats and rabbits in classical reproductive and teratogenic studies. Significant untoward effects were not observed. One litter of 14 pups from a rat treated with 45 mg/kg between days 6 to 15 of gestation had 6 malformed pups. Malformations included kinky tails, a short upper jaw, and renal agenesis. Two pups in another litter had unilateral micropthalmia. An association with treatment was considered doubtful.

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PART III CONSUMER INFORMATION

Dantrium® Capsules
Dantrolene Sodium Capsules, Mfr. Std.

This leaflet is part III of a three-part "Product Monograph" published when Dantrium was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Dantrium. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
- Relief of chronic spasticity (spasms and stiffness) of skeletal muscle in conditions such as spinal cord injury, cerebral palsy, multiple sclerosis and stroke.
- Pre-operative management of surgical patients who are susceptible to malignant hyperthermia (MH; a genetic muscle condition where sustained muscle contractions and/or life-threatening reactions may occur when susceptible individuals are exposed to specific anaesthetic drugs. In very rare cases, MH reactions may occur without anaesthetic).
- Follow-up management of patients treated with intravenous dantrolene.

What it does:
Dantrium reduces excessive muscle contractions.

When it should not be used:
Dantrium is not suitable for everyone. It should not be used:
- If you are allergic to Dantrium (dantrolene sodium) or any of its ingredients (See What the important nonmedicinal ingredients are)
- If muscle tension is needed to maintain function (e.g., sustaining upright posture and balance)
- If you have reduced lung capacity (e.g., obstructive pulmonary disease)
- If you have active liver disease (e.g., hepatitis, cirrhosis)

Use of Dantrium to relieve muscle spasms from rheumatic disorders is not recommended.

What the medicinal ingredient is:
Dantrolene Sodium

What the important nonmedicinal ingredients are:
edible black ink, gelatin, iron oxide red, iron oxide yellow, lactose, magnesium stearate, starch, talc, titanium dioxide.

What dosage forms it comes in:
- Dantrium 25 mg is an orange and tan-brown capsule coded with 1 black bar and DANTRIUM 25 mg 0149 0030.
- Dantrium 100 mg is an orange and tan-brown capsule coded with 3 black bars and DANTRIUM 100 mg 0149 0033.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
- Dantrium has a potential for serious liver disease, sometimes fatal. For symptoms of liver disease see **Side Effects And What To Do About Them**.
- Populations that may be at greater risk include women, patients over the age of thirty, patients taking other medication(s) or taking other therapies that have the potential to cause liver damage.
- Dantrium has been shown to cause cancer in rats. Thus a potential for Dantrium to cause cancer in humans can not be ruled out. Discuss with your doctor.

BEFORE you use Dantrium talk to your doctor or pharmacist if:
- You have liver disease
- You have heart disease
- You have lung disease
- You are using rehabilitation devices such as wheelchair, crutches, braces, walkers or canes
- You are allergic to drugs that are chemically related to Dantrium
- You are pregnant or you may become pregnant
- You are nursing
- The patient is a child under 5 years of age. Dantrium is usually not recommended in this age group.

If you are taking this medication for a long period of time, you will need to go for regular testing of your blood, liver and kidneys.

This medicine may make your skin more sensitive to sunlight. It is important to use a sunscreen when outdoors and avoid the use of sunlamps.

You should not drive, operate machinery or engage in activities that require unimpaired judgement and coordination during the first week of therapy.

INTERACTIONS WITH THIS MEDICATION

If taken with some other medicines, the effects of Dantrium or the effects of other medicines may be affected. Please check with your doctor or pharmacist before taking other medications with Dantrium.

Drugs that may interact with Dantrium include alcohol, some muscle relaxants, tranquilizing agents, antihistamines, sedatives, tranquilizers, pain medication, seizure medication, calcium channel blockers or anaesthetics.

It is important to tell your doctor what other medications you are taking, even if the medicine does not require a prescription (including vitamins and herbal supplements).

PROPER USE OF THIS MEDICATION

Usual dose:
The dosage of Dantrium will be tailored to meet the needs of each patient.

Adults: The initial dose is 25 mg once per day and may be increased, as needed and tolerated, to a maximum of 100 mg four times a day.

Children: The dose is determined using body weight. The usual starting dose is 0.5 mg/kg of body weight twice a day and may be increased as needed and tolerated to a maximum of 3 mg/kg four times daily.

This medicine has been prescribed to you by your doctor. Do not share this medication with anyone else.

Follow the doctor's instruction about how and when you should take your medication. Your doctor may adjust your dose to get the best effect. Speak with your doctor if you are concerned about the dose.

If you are taking care of a child who has been prescribed Dantrium, follow the doctor's instructions carefully.

Overdose:
If you take more than the recommended number of capsules, immediately contact your doctor or pharmacist or go to the nearest emergency department.

Missed Dose:
If you miss a dose, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. DO NOT take two doses at once to make up for a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with any medication, side effects may occur with Dantrium use. The most common side effects include diarrhoea, drowsiness, weakness, dizziness, feeling ill and fatigue.

Other commonly reported side effects include loss of appetite, abdominal pain, nausea, vomiting, skin rash, fever and chills, headache.

Rarely reported side effects include constipation, difficulty swallowing, sweating, increased urinary frequency.

IMPORTANT SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Common (more than 1 in 100)			
Symptoms of liver problems including: pale stools, yellow skin or eyes, itching and rash, loss of appetite, nausea and vomiting			√
Chest pain, palpitations/fluttering of the heart, difficulty breathing			√
Seizure, speech and visual disturbance			√
Uncommon (less than 1 in 100)			
Mental depression or confusion		√	
Worsening of heart failure			√

This is not a complete list of side effects. For any other side effects or health concerns while taking Dantrium, contact your doctor or pharmacist.

HOW TO STORE IT

Dantrium should be stored at room temperature (15 - 30° C).

The expiry date of this medication is printed on the label. Do not use the medication after this date.

This medicine is for you or the child you are taking care of. Only a doctor can prescribe it for you or your child.

Never give it to others. It may harm them.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals is available by contacting the distributor, Methapharm Inc. at:
1-800-287-7686

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