PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[Pr]DANTRIUM® CAPSULES

Dantrolene Sodium Capsules
Capsules, 25 mg, Oral
Mfr. Std.

Skeletal Muscle Relaxant

Endo Par Innovation Company, LLC.
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Chestnut Ridge
NY, 10977, USA

Importer/Distributor:
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DANTRIUM® is a registered trademark of Par Sterile Products, LLC.

RECENT MAJOR LABEL CHANGES

Section	Date
None	N/A

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DANTRIUM CAPSULES (dantrolene sodium capsules) 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 CAPSULES is not indicated in the relief of skeletal muscle spasms due to rheumatic disorders.

1.1 Pediatrics

Pediatrics (5-18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DANTRIUM CAPSULES in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use in this subpopulation (see 7.1.3 Pediatrics).

Pediatrics (<5 years of age): Since there is insufficient experience with the use of DANTRIUM CAPSULES in young children, the drug is usually not recommended in this age group.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety and effectiveness (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

DANTRIUM CAPSULES 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 6 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 (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal).
- Patients with compromised pulmonary function, particularly those with obstructive pulmonary disease.

- Patients with active hepatic disease, such as hepatitis and cirrhosis (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Hepatotoxicity

DANTRIUM CAPSULES (dantrolene sodium capsules) 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 CAPSULES may exacerbate pre-existing liver dysfunction. DANTRIUM CAPSULES 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 CAPSULES is recommended and if after 45 days no observable benefit is evident, DANTRIUM CAPSULES should be discontinued. The lowest possible effective dose for the individual patient should be prescribed (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Carcinogenicity

There is evidence of low-grade carcinogenicity activity of DANTRIUM CAPSULES in rats. Thus, potential carcinogenicity in humans cannot be disregarded (see 7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

4 DOSAGE AND ADMINISTRATION

4.1 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 CAPSULES should be discontinued if benefits are not evident within 45 days (see 3 SERIOUS WARNINGS AND PRECAUTIONS, Hepatotoxicity).
- Prior to the administration of DANTRIUM CAPSULES, 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 CAPSULES. See 10 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 CAPSULES 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.

4.2 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 (5-18 years of age): 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 7.1.3 Pediatrics).

4.5 Missed Dose

Patients should be instructed that if they miss a dose of DANTRIUM CAPSULES, 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.

5 OVERDOSAGE

Symptoms and Signs

There is no known constellation of symptoms with acute overdose of DANTRIUM CAPSULES. 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 CAPSULES 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 CAPSULES overdosage is not known.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsules 25 mg	Edible black ink, FD&C yellow 6, gelatin, iron oxide red, iron oxide yellow, lactose, magnesium stearate, sodium lauryl sulfate, starch, talc, titanium dioxide

DANTRIUM CAPSULES is available in opaque orange and brown capsules of 25 mg (opaque orange cap and opaque light tan to brown body). The capsules are printed with "Dantrium" "25 mg" on the cap and "0149" "0030" and a single coding bar on the body. DANTRIUM CAPSULES is supplied in bottles of 100's.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis
Toxicity studies in animals provided evidence of low-grade carcinogenic activity of DANTRIUM CAPSULES in the rat (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity). 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 CAPSULES as recommended above (see 3 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 CAPSULES has not yet been established.

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

Driving and Operating Machinery
Dantrolene sodium 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 CAPSULES therapy.

Hepatic/Biliary/Pancreatic
Fatal and non-fatal hepatitis have occurred at various dosage levels of dantrolene sodium. 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 CAPSULES 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 sodium 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 3 SERIOUS WARNINGS AND PRECAUTIONS, Hepatotoxicity.

Monitoring and Laboratory Tests
Liver function tests should be performed before therapy and during therapy at adequate intervals (see 3 SERIOUS WARNINGS AND PRECAUTIONS, Hepatotoxicity).

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

Musculoskeletal
Although subjective weakness attributable to DANTRIUM CAPSULES is usually transient, some patients feel excessively weak as long as DANTRIUM CAPSULES 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 CAPSULES should be discontinued if the weakness persists and interferes with the use of a rehabilitation device.

Respiratory
DANTRIUM CAPSULES is contraindicated in patients with impaired pulmonary function (see 2 CONTRAINDICATIONS).

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 CAPSULES, it is possible that in some subjects the drug might evoke a phototoxic response.

7.1 Special Populations

7.1.1 Pregnant Women
The safety of DANTRIUM CAPSULES 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 sodium crosses the placenta.

7.1.2 Breast-feeding
DANTRIUM CAPSULES should not be used in nursing mothers. Dantrolene sodium has been detected in human milk.

7.1.3 Pediatrics
Pediatrics (5-18 years of age): In view of the 3 SERIOUS WARNINGS AND PRECAUTIONS, it is particularly important to assess risk acceptability before DANTRIUM CAPSULES is used in pediatric patients.

Pediatrics (<5 years of age): Since there is insufficient experience with the use of DANTRIUM CAPSULES in young children, the drug is usually not recommended in this age group.

7.1.4 Geriatrics
Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety and effectiveness. Spontaneous reports also suggest a higher proportion of hepatic events with fatal outcome in elderly patients (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview
Side effects most frequently reported were drowsiness, weakness, dizziness, malaise, fatigue and diarrhea. These effects were generally transient and may be avoided with initial low doses and a gradual increase to optimal doses. Diarrhea 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

CNS: Speech and visual disturbances, seizure, headache, lightheadedness, taste alterations,

mental depression, confusion, nervousness, diplopia and insomnia

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 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)

Hypersensitivity: Pleural effusion with pericarditis or with associated eosinophilia

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

Musculoskeletal: Myalgia, backache

Respiratory: Respiratory depression

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

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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Alterations of liver function studies tests attributable to DANTRIUM CAPSULES have been observed. It is therefore advisable to perform liver function tests before and during therapy (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

Dantrolene sodium causes dizziness, drowsiness, and weakness; alcohol and other central nervous system (CNS) medications may intensify this effect.

9.4 Drug-Drug Interactions

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

Although the primary pharmacologic effect of DANTRIUM CAPSULES 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 sodium and concomitant calcium channel blockers.

9.5 Drug-Food Interactions
Interactions with food have not been established.

9.6 Drug-Herb Interactions
Interactions with herbs have not been established.

9.7 Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action
Recordings of muscle tensions and electrical activity in both animal and man suggest that dantrolene sodium has a direct inhibitory effect on the development of contractile tension. Spastic patients receiving DANTRIUM CAPSULES 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 dantrolene sodium beyond the myoneural junction. Total paralysis does not occur since the dantrolene sodium-induced change in the contractile state of skeletal muscle is limited in magnitude. The reduction in contractile activity accounts for the ability of dantrolene sodium to diminish spasticity resulting from pathological states associated with a hyperactive stretch reflex.

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

10.2 Pharmacodynamics
Dantrolene sodium causes marked, dose-dependent skeletal muscle relaxation in laboratory animals with a long duration of action. The pharmacologic profile of dantrolene sodium 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 in coordination with dantrolene sodium 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 dantrolene sodium.

Various studies both *in vivo* and *in vitro* demonstrated the apparent selectivity of action of dantrolene sodium 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 dantrolene sodium in several animal studies.

It has been shown that dantrolene sodium 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 dantrolene sodium acts on skeletal muscle by altering the Ca^{++} release mechanisms. Such an action could explain the apparent specificity of dantrolene sodium for skeletal muscle.

10.3 Pharmacokinetics

Absorption: Absorption of DANTRIUM CAPSULES 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.

Distribution: Based on assays of whole blood and plasma, slightly greater amounts of dantrolene sodium are associated with red blood cells than with the plasma fraction of blood.

Metabolism: Metabolism is rapid via hepatic microsomal enzymes. The major metabolites in humans are a 5-hydroxy analog and an acetamino analog.

Animal studies have indicated that dantrolene sodium 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 CAPSULES. Maximal blood levels following oral administration are reached in approximately 1 hour. In dogs approximately 40% of an i.v. dose of dantrolene sodium 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.

Elimination: Urinary excretion of dantrolene sodium 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. Dantrolene sodium is also removed by biliary excretion.

11 STORAGE, STABILITY AND DISPOSAL

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

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: dantrolene sodium

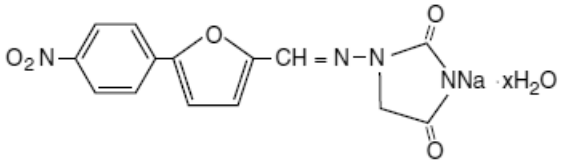
Chemical name: 1-[5-(p-nitrophenyl)-furfurylidene] amino hydantoin sodium hydrate

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

399.29 (hydrous)

336.23 (anhydrous)

Structural formula:



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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

DANTRIUM CAPSULES 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 CAPSULES. The extent to which DANTRIUM CAPSULES 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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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.

Carcinogenicity: 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. Dantrolene sodium 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®-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.

Genotoxicity: The genotoxicity potential on which the original indication was authorized is not available.

Reproductive and Developmental Toxicology: 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]DANTRIUM® CAPSULES
dantrolene sodium capsules

Read this carefully before you start taking **DANTRIUM CAPSULES** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DANTRIUM CAPSULES**.

Serious Warnings and Precautions

Liver problems:

- DANTRIUM CAPSULES may cause serious liver problems such as hepatotoxicity (damage to the liver) and hepatitis (inflammation of the liver). It can also make pre-existing liver problems worse. Therefore, DANTRIUM CAPSULES should NOT be used:
  - to treat medical conditions other than those recommended; and
  - in patients who currently have liver problems (e.g., cirrhosis, hepatitis).
- Hepatitis has occurred at various doses and was seen most frequently after the second month of treatment. It can even lead to death, especially in the elderly.
- Your risk of experiencing serious liver problems increases when you take DANTRIUM CAPSULES, especially if you:
  - are female;
  - are over 30 years of age;
  - take high doses of DANTRIUM CAPSULES, even for a short time;
  - take certain medicines at the same time, especially ones that are known to cause serious liver problems.
- You will have regular visits with your healthcare professional before and during your treatment with DANTRIUM CAPSULES to monitor the health of your liver.
- Your healthcare professional may prescribe you DANTRIUM CAPSULES for a trial period to determine if it is right for you. They will give you the lowest possible dose needed for your treatment. If your condition does not improve within the first 45 days of treatment, tell your healthcare professional. They should stop your treatment.

See the **Serious side effects and what to do about them** table for more information on this and other serious side effects.

Cancer: DANTRIUM CAPSULES may increase your risk of cancer. Your healthcare professional will assess your risk and decide if the expected benefits of taking DANTRIUM CAPSULES outweigh the possible risks to your health.

What is DANTRIUM CAPSULES used for?
DANTRIUM CAPSULES is used in adults and children (5 to 18 years of age):

- to relieve chronic muscle stiffness and cramping (spasms) caused by certain medical problems such as cerebral palsy, multiple sclerosis, stroke, and injuries to the spine.
- before surgery or anesthesia to prevent a medical problem called malignant hyperthermia (MH) in patients at risk. MH is a severe reaction that may occur when susceptible individuals are exposed to certain anesthetic medicines. It can be life-threatening. MH may involve severe muscle contractions, a dangerously high body temperature, a rapid heartbeat, and other symptoms. Your risk of MH increases if you have certain gene mutations.
- as follow-up management after being treated with intravenous dantrolene sodium.

How does DANTRIUM CAPSULES work?
DANTRIUM CAPSULES belongs to a group of medicines called skeletal muscle relaxants. It reduces excessive muscle contractions.

What are the ingredients in DANTRIUM CAPSULES?
Medicinal ingredient: dantrolene sodium
Non-medicinal ingredients: edible black ink, FD&C yellow 6, gelatin, iron oxide red, iron oxide yellow, lactose, magnesium stearate, sodium lauryl sulfate, starch, talc, and titanium dioxide

DANTRIUM CAPSULES comes in the following dosage forms:
Capsules: 25 mg

Do not use DANTRIUM CAPSULES if:

- you are allergic to dantrolene sodium or any other ingredients in DANTRIUM CAPSULES.
- muscle tension allows you to keep an upright posture, to balance during movement, or help you carry out your daily activities.
- you have reduced lung capacity particularly due to an obstructive pulmonary disease (e.g., chronic obstructive pulmonary disease (COPD), emphysema, asthma, chronic bronchitis or cystic fibrosis).
- you have active liver problems (e.g., hepatitis, cirrhosis).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DANTRIUM CAPSULES. Talk about any health conditions or problems you may have, including if you:

- have heart problems
- have lung problems
- have a history of liver problems
- are allergic to other medicines of the hydantoin family, including phenytoin, fosphenytoin, nitrofurantoin, or nilutamide
- use rehabilitation devices such as wheelchair, crutches, braces, walkers or canes

- are pregnant or planning to become pregnant
- are breastfeeding or planning to breastfeed

Other warnings you should know about:
Photosensitivity: You may become sensitive to the sun while taking DANTRIUM CAPSULES. You should reduce your exposure to sunlight until you know how you respond. Tell your healthcare professional if you notice any photosensitivity.

Muscle weakness: You may feel very weak while taking DANTRIUM CAPSULES. This usually lasts only for a short time. Tell your healthcare professional if your muscle weakness persists or interferes with the use of rehabilitation devices such as wheelchairs, crutches, braces, walkers, or canes.

Pregnancy: Dantrolene sodium, the active ingredient in DANTRIUM CAPSULES, can cross the placenta. It is not known if it can harm an unborn baby. DANTRIUM CAPSULES should not be taken during pregnancy unless your healthcare professional has determined the expected benefits outweigh the possible risks to your health and that of your baby. Tell your healthcare professional right away if you become pregnant or think you might be pregnant during your treatment with DANTRIUM CAPSULES.

Breastfeeding: Dantrolene sodium, the active ingredient in DANTRIUM CAPSULES, can pass into breast milk. It is not known if it can harm a breastfed baby. Do not breastfeed while taking DANTRIUM CAPSULES. Talk to your healthcare professional about the best way to feed your baby during this time.

Driving and using machines: DANTRIUM CAPSULES can cause dizziness, drowsiness and weakness. Alcohol and medicines that affect the central nervous system (CNS) may increase this effect. You should not drive or do tasks that require special attention during the first week of your treatment with DANTRIUM CAPSULES.

Check-ups and testing: You will have regular visits with your healthcare professional, before and during your treatment. They may do tests to monitor the health of your kidneys and liver, and the profile of your blood.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with DANTRIUM CAPSULES:
- other muscle relaxants
- anesthetics (used during surgery and other procedures)
- sedatives and tranquilizers (used to treat anxiety, panic and sleep disorders)
- seizure medications (used to prevent and treat seizures)
- pain medications
- antihistamines (used to treat allergies)

- calcium channel blockers (used to lower blood pressure and relieve chest pain)
- alcohol

How to take DANTRIUM CAPSULES:

- Before taking DANTRIUM CAPSULES, you and your healthcare professional will decide on a goal you would like to reach during your treatment. This may include regaining or keeping a certain function. This includes an exercise program, the use of braces, certain movements or physical abilities, etc.
- During your treatment with DANTRIUM CAPSULES, your healthcare professional may gradually increase your dose. They will give you the lowest possible dose needed to reach the best outcome.
- Take DANTRIUM CAPSULES exactly as your healthcare professional has told you. If you are taking care of a child for whom DANTRIUM CAPSULES have been prescribed, follow the healthcare professional's instructions carefully.
- Your treatment may be discontinued if no benefit is seen within the first 45 days. This is to prevent potential liver damage associated with long-term use of DANTRIUM CAPSULES.
- This medicine has been prescribed for you by your healthcare professional. Do not share this medicine with anyone else.

Usual dose:

Your healthcare professional will decide on the dose that is right for you or your child.

- **Adults:** The initial dose is 25 mg once a day. Your dose may be increased as needed and tolerated to a maximum of 100 mg four time a day.
- **Children (5 to 18 years of age):** Your child's dose will be determined using their body weight. The usual starting dose is 0.5 mg per each kilogram they weight twice a day. Their dose may be increased as needed and tolerated to a maximum of 3 mg for each kilogram they weight four times a day.

Overdose:

Signs of an overdose with DANTRIUM CAPSULES may include:

- muscle weakness
- altered state of consciousness (e.g., lack of energy or coma)
- vomiting
- diarrhea

If you think you, or a person you are caring for, have taken too much DANTRIUM CAPSULES, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you have forgotten or missed a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and take your next dose at the usual time. Do not double the doses.

What are possible side effects from using DANTRIUM CAPSULES?
These are not all the possible side effects you may have when taking DANTRIUM CAPSULES. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- feeling drowsy, weak, dizzy, nervous, ill or fatigued
- diarrhea, constipation, abdominal cramps or pain
- nausea, vomiting
- difficulty swallowing
- headache
- fever, chills
- a heart rate that is faster than normal
- back pain, muscle aches and pain
- difficulty falling or staying asleep
- skin problems such as itchy skin, hives, acne- or eczema-like rashes
- difficulty getting or keeping an erection
- abnormal hair growth
- sweating
- problems with vision
- teary eyes
- changes in speech such as slurring
- changes in tastes
- confusion (feeling disoriented and/or distracted)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Liver problems: jaundice (yellowing of the skin or whites of eyes), unusual dark urine, light-colored stool, loss of appetite, nausea, vomiting, abdomen pain or swelling, unusual tiredness, mental disorientation or confusion, sleepiness, coma			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Pleural effusion (fluid around the lungs): chest pain that may get worse when you breathe, cough, sneeze or lie flat, shortness of breath that may get worse if you lie flat, cough, fever. May be accompanied with an abnormal heartbeat, general feeling of weakness or being sick, abdominal or leg swelling, skin rash or itchy skin			√
Seizures (fit): loss of consciousness with uncontrollable shaking			√
UNCOMMON			
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide. If you have a history of depression, your depression may become worse		√	
Worsening of heart failure: shortness of breath, feeling weak or tired, rapid weight gain, unusual swelling of the legs, feet, hands or abdomen, cough, reduced ability to do activities or exercises			√
UNKNOWN FREQUENCY			
Changes in blood pressure: dizziness, headache, vision		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
problems, shortness of breath, nausea, vomiting, fainting			
Gastrointestinal bleeding in the stomach or bowels: black, tarry stool, blood in the stool		√	
Intestinal obstruction (blockage that stops or impairs passage of contents of intestines): cramping pain in abdomen that may begin suddenly, bloating, loss of appetite, pain that comes and goes but will then last, nausea and vomiting, constipation or diarrhea		√	
Phlebitis (swelling of a vein): pain, tenderness, redness or swelling		√	
Respiratory depression (also known as hypoventilation): slow, shallow or weak breathing, blue lips, fingers, toes, confusion, headaches			√
Urinary problems: inability to pass or empty the bladder, painful urination, lack of bladder control, frequent urination (including during the night**)**		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store DANTRIUM CAPSULES at room temperature (15°C - 30°C).
- Do not use the medication after the expiry date printed on the label.
- Keep out of reach and sight of children.

If you want more information about DANTRIUM CAPSULES:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the distributor's website www.paladinlabs.com, or by calling 1-888-867-7426.

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