PRODUCT MONOGRAPH

PrENDANTADINE*

amantadine hydrochloride, capsules USP, 100 mg

Antiparkinsonian Agent

Bristol-Myers Squibb Canada
Montreal, Canada

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THERAPEUTIC CLASSIFICATION

Antiparkinsonian Agent

ACTION AND CLINICAL PHARMACOLOGY

While the mechanism of action of ENDANTADINE (amantadine hydrochloride) in the treatment of Parkinson's syndrome and drug-induced extrapyramidal reactions is not known, it is believed to release brain dopamine from nerve endings making it more available to activate dopaminergic receptors. The drug does not possess anticholinergic activity in animal tests at doses similar to those used clinically.

The antiviral activity of ENDANTADINE for the prophylaxis of Asian (A2) influenza in humans appears not to be related to the possible mode of action of this drug in Parkinson's syndrome.

In man, ENDANTADINE is readily absorbed, passes the blood-brain barrier and appears in the saliva and nasal secretions. Amantadine hydrochloride can be detected in the blood and cerebrospinal fluid at relatively low, but dose-related, levels. No evidence of metabolites has been found and 90% or more of the dose can be recovered in the urine unchanged.

After oral administration of a single dose of 100 mg, maximum blood levels are reached in approximately 4 hours, based on mean time of the peak urinary excretion rate; the peak excretion rate is approximately 5 mg/hour; the mean half-life of the excretion rate approximates 15 hours.

Compared with otherwise healthy adult individuals, the clearance of amantadine is significantly reduced in adult patients with renal insufficiency. The elimination half-life increases two to three fold when creatinine clearance is less than 40 mL/min./1.73m^2 and averages eight days in patients on chronic maintenance hemodialysis.

The renal clearance of amantadine is reduced and plasma levels are increased in otherwise healthy elderly patients age 65 years and older. The drug plasma levels in elderly patients receiving 100 mg daily have been reported to approximate those determined in younger adults taking 200 mg daily. Whether these changes are due to the normal decline in renal function or other age factors is not known.

INDICATIONS AND CLINICAL USE

ENDANTADINE (amantadine hydrochloride) is useful in the treatment of Parkinson's syndrome and in the short-term management of drug-induced extrapyramidal symptoms.

In Parkinson's syndrome, ENDANTADINE has been used alone and in combination with anticholinergic antiparkinsonian drugs and with levodopa. The final therapeutic benefit seen with ENDANTADINE is significantly less than that seen with levodopa. The maximal therapeutic benefit to be obtained with ENDANTADINE is usually seen within 1 week. However, initial benefits may diminish with continued dosing.

ENDANTADINE is useful as an adjunct in patients who do not tolerate optimal doses of levodopa alone or in combined therapy with a decarboxylase inhibitor. In these patients, the addition of ENDANTADINE may result in better control of Parkinson's syndrome and may help to smooth out fluctuations in performance.

The comparative efficacy of ENDANTADINE and anticholinergic antiparkinsonian drugs has not yet been established. When ENDANTADINE or anticholinergic antiparkinsonian drugs are each used with marginal benefit, concomitant use may permit the same degree of control, often with a lower dose of the anticholinergic medication.

ENDANTADINE is effective in reducing severity or abolishing drug-induced extrapyramidal reactions including parkinsonism syndrome, dystonia and akathisia. ENDANTADINE is not effective in the management of tardive dyskinesia.

Although anticholinergic-type side effects have been noted with ENDANTADINE when used in patients with drug-induced extrapyramidal reactions, there appears to be a lower incidence of these side effects than that observed with anticholinergic antiparkinsonian drugs.

Antiparkinsonian agents should not usually be used prophylactically during neuroleptic administration. However, they may be given when needed to suppress extrapyramidal symptoms. Therefore, ENDANTADINE may be used in the management of extrapyramidal symptoms which cannot be controlled by reduction of neuroleptic dosage, but should be discontinued as soon as it is no longer required. ENDANTADINE should be withdrawn after a period of time to determine whether there is recrudescence of extrapyramidal symptoms.

CONTRAINDICATIONS

ENDANTADINE (amantadine hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

A small number of suicidal attempts, some of which have been fatal, have been reported in patients treated with amantadine hydrochloride. The incidence of suicidal attempts is not known and the pathophysiologic mechanism is not understood. Suicidal attempts and suicidal ideation have been reported in patients with and without prior history of psychiatric illness. Amantadine hydrochloride can exacerbate mental problems in patients with a history of psychiatric disorders or substance abuse.

Patients who attempt suicide may exhibit abnormal mental states which include disorientation, confusion, depression, personality changes, agitation, aggressive behaviour, hallucinations, paranoia, other psychotic reactions, and somnolence or insomnia. Because of the possibility of serious adverse effects, caution should be observed when prescribing ENDANTADINE (amantadine hydrochloride) to patients being treated with drugs having CNS effects, or for whom the potential risks outweigh the benefit of treatment. Because some patients have attempted suicide by overdosing with amantadine, prescriptions should be written for the

smallest quantity consistent with good patient management.

Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity.

Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving amantadine hydrochloride.

Patients with Parkinson's disease improving on ENDANTADINE should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis.

Patients receiving ENDANTADINE who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness and adequate motor coordination are important.

PRECAUTIONS

General

ENDANTADINE (amantadine hydrochloride) should not be discontinued abruptly since a few patients with Parkinson's syndrome experienced a parkinsonian crisis, ie., sudden marked clinical deterioration, when this medication was suddenly stopped.

Neuroleptic Malignant Syndrome (NMS)

Sporadic cases of possible Neuroleptic Malignant Syndrome (NMS) have been reported in association with dose reduction or withdrawal of amantadine hydrochloride therapy. NMS is neurologic findings including muscle rigidity, involuntary movements, altered consciousness; other disturbances such as autonomic dysfunction, tachycardia, tachypnea, hyper- or hypotension; laboratory findings such as creatinine phosphokinase elevation, leukocytosis, and increased serum myoglobin.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include:
1) intensive symptomatic treatment and medical monitoring, and
2) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

Use in Patients with Special Diseases and Conditions

Because ENDANTADINE (amantadine hydrochloride) is not metabolized and is mainly excreted in the urine, it may accumulate in the plasma and in the body when renal function

declines. The dose of ENDANTADINE should be reduced in patients with renal impairment and in patients who are 65 years of age or older. (See DOSAGE AND ADMINISTRATION). The dose of ENDANTADINE may need careful adjustment in patients with congestive heart failure, peripheral edema, or orthostatic hypotension.

Care should be exercised when administering ENDANTADINE to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Rare instances of reversible elevation of liver enzyme levels have been reported in patients receiving amantadine hydrochloride, though a specific relationship between the drug and such changes has not been established.

Use in Pregnancy

Amantadine hydrochloride has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day, approximately 12 times the recommended human dose, but not at 37 mg/kg/day. Embryotoxic and teratogenic drug effects were not seen in rabbits that received up to 25 times the recommended human dose.

There are no adequate and well controlled studies in pregnant women. Therefore, ENDANTADINE should not be used in women with childbearing potential, unless in the opinion of the physician, the expected benefit to the patient outweighs the possible risk to the fetus (see TOXICOLOGY - Effects on Reproduction).

Nursing Mothers

Since amantadine is secreted in human milk, the use of ENDANTADINE is not recommended in nursing mothers.

Pediatric Use

The safety and efficacy of use of ENDANTADINE in neonates and infants less than 1 year old have not been established.

Skin

Some epidemiological studies have shown that patients with Parkinson's disease have a higher risk (perhaps 2- to 4-fold higher) of developing melanoma than the general population. Whether the observed increased risk was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, was unclear. ENDANTADINE* is one of the drugs used to treat Parkinson's disease. Although ENDANTADINE* has not been associated with an increased risk of melanoma specifically, its potential role as a risk factor has not been systematically studied. Patients treated with ENDANTADINE* should be made aware of these results and should undergo periodic dermatologic screening.

Drug Interactions

The dose of anticholinergic drugs or of ENDANTADINE should be reduced if atropine-like effects appear when these drugs are used concurrently.

Careful observation is required when ENDANTADINE is administered concurrently with central nervous system stimulants.

ADVERSE REACTIONS

Adverse reactions reported below have occurred in patients while receiving ENDANTADINE (amantadine hydrochloride) alone or in combination with anticholinergic anti-parkinson drugs and/or levodopa.

The adverse reactions reported most frequently (5-10%) are: nausea, dizziness (lightheadedness) and insomnia.

Less frequently reported (1-5%) are: depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension, headache, somnolence, nervousness, dream abnormality, agitation, dry nose, diarrhea and fatigue.

Infrequently occurring adverse reactions (0.1-1%) are: congestive heart failure, psychosis, urinary retention, dyspnea, skin rash, vomiting, weakness, slurred speech, euphoria, confusion, thinking abnormality, amnesia, hyperkinesia, hypertension, decreased libido, and visual disturbance, including punctuate subepithelial or other corneal opacity, corneal edema, decreased visual acuity, sensitivity to light, and optic nerve palsy.

Rarely occurring adverse reactions (less than 0.1%) are: instances of convulsion, leukopenia, neutropenia, eczematoid dermatitis and oculogyric episodes. Other rare occurring adverse reactions are: suicidal attempt, suicide, and suicidal ideation (see WARNINGS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Deaths have been reported from overdose with amantadine hydrochloride. The lowest reported acute lethal dose was 2 grams. An elderly patient with Parkinson's syndrome who took an overdose of 2.8 g of amantadine hydrochloride in a suicidal attempt, developed acute toxic psychosis, urinary retention, and a mixed acid-base disturbance. The toxic psychosis was manifested by disorientation, confusion, visual hallucinations and aggressive behavior. Convulsions did not occur, possibly because the patient had been receiving phenytoin prior to the acute ingestion of amantadine hydrochloride.

There is no specific antidote. Slowly administered intravenous physostigmine in 1 and 2 mg doses at 1 to 2 hour intervals in an adult, and 0.5 mg doses at 5 to 10 minute intervals in a child up to a maximum of 2 mg/hour, have been reported to be effective in the control of central nervous system toxicity caused by amantadine hydrochloride. For acute overdosing, general supportive measures should be employed, along with immediate gastric lavage or induction of emesis. Fluids should be forced, and if necessary, given intravenously.

Hemodialysis does not remove significant amounts of amantadine hydrochloride in patients with renal failure; a four hour hemodialysis removed 7 to 15 mg after a single 300 mg oral dose.

The pH of the urine has been reported to influence the excretion rate of ENDANTADINE (amantadine hydrochloride). Since the excretion rate of amantadine hydrochloride increases rapidly when the urine is acidic, the administration of urine acidifying fluids may increase the elimination of the drug from the body. The blood pressure, pulse, respiration and temperature should be monitored. The patient should be observed for the possible development of arrhythmias, hypotension, hyperactivity, and convulsions; if required, appropriate therapy should

be administered. The blood electrolytes, urine pH and urinary output should be monitored. If there is no record of recent voiding, catheterization should be done. The possibility of multiple drug ingestion by the patient should be considered.

DOSAGE AND ADMINISTRATION

Parkinson's Syndrome

The initial dose of ENDANTADINE (amantadine hydrochloride) is 100 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinsonian drugs. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily. When ENDANTADINE and levodopa are initiated concurrently, ENDANTADINE should be held constant at 100 mg daily or twice daily while the daily dose of levodopa is gradually increased to optimal dose. When used alone, the usual dose of ENDANTADINE is 100 mg twice a day.

Patients whose responses are not optimal with ENDANTADINE at 200 mg daily may benefit from an increase to 300 mg daily in divided doses. Patients who experience a fall-off of effectiveness may regain benefit by increasing the dose to 300 mg daily; such patients should be supervised closely by their physicians.

Drug-Induced Extrapyramidal Symtoms

The usual dose of ENDANTADINE is 100 mg twice a day. Occasionally, patients whose responses are not optimal with ENDANTADINE at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.

In the Presence of Impaired Renal Function

The following table outlines the recommended dosage adjustments dependent upon creatinine clearance, based upon the current National Advisory Committee on Immunization (NACI) Canada Communicable Disease Report, May 29, 1992.

Creatinine Clearance ($mL/min/1.73m^2$)	**Dosage**
≥ 80	100 mg twice daily
60 - 79	Alternating daily doses of 200 and 100 mg
40 - 59	100 mg once daily
30 - 39	200 mg twice weekly
20 - 29	100 mg thrice weekly
10 - 19	Alternating weekly doses of 200 and 100 mg

The recommended dosage for patients on hemodialysis is 200 mg every 7 days.

PHARMACEUTICAL INFORMATION

Drug Substance

Trade Name: ENDANTADINE

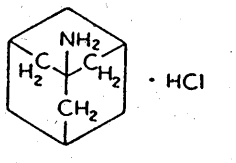
Proper Name: amantadine hydrochloride, USP

Chemical Name: 1 - adamantanamine hydrochloride

Molecular Formula: $C_{10}H_{17}N \cdot HCl$

Molecular Weight: 187.71

Structural Formula:



Description

Amantadine hydrochloride is a stable, white crystalline powder, freely soluble in water, and soluble in alcohol and in chloroform.

Composition

The fill material of ENDANTADINE capsules contains:

Amantadine Hydrochloride, USP
Hydrogenated Vegetable Oil, NF
Lecithin, unbleached
Soya Bean Oil, USP
Vegetable Shortening
Yellow Wax, NF

The shell material of ENDANTADINE capsules contains:

FD & C Red #40
Gelatin, NF
Glycerin, USP
Methyl Paraben, NF
Propyl Paraben, NF
Purified Water, USP
Titanium Dioxide, USP

Storage

Store at controlled room temperature (15° to 30°C) in a tightly closed container.

DOSAGE FORMS

Capsules

Each red, soft gelatin capsule contains 100 mg of amantadine hydrochloride, USP. Bottles of 100.

PHARMACOLOGY

The available evidence from animal studies points to an interaction with dopamine and perhaps with other catecholamines within the brain as the major mode of action of amantadine hydrochloride in the treatment of parkinsonism. Although the intimate details of the mechanism of action are not fully understood, the most likely possibilities are that amantadine hydrochloride (1) directly releases dopamine and perhaps other catecholamines within the brain, (2) increases their rate of synthesis, or (3) assists in their release in response to on-going neural activity.

Animal data indicate that amantadine hydrochloride does not exert its antiparkinson effect through an anticholinergic mechanism. Amantadine hydrochloride (1) was non-selective and essentially inactive against acetylcholine-induced contractions of guinea pig ileum, (2) did not significantly block the vasodepressor response to acetylcholine in dogs, and (3) failed to antagonize tremors induced in mice by oxotremorine.

In animals, amantadine hydrochloride caused several pharmacologic effects at relatively high doses. Signs of motor activity stimulation (increased spontaneous motor activity and antagonism of tetrabenazine-induced sedation) occurred in mice at oral doses of 35-40 mg/kg and above. A transient vasodepressor effect, cardiac arrhythmias and a weak ganglionic-blocking effect in dogs were observed following intravenous doses of 13.5 mg/kg or above. EEG activation has been reported in the rat and rabbit with high parenteral doses.

In addition, the observations summarized in the table below have afforded evidence that amantadine hydrochloride causes norepinephrine release and blockade of norepinephrine re-uptake at peripheral autonomic neuron storage sites.

Response	Species	Amantadine Hydrochloride	
		Dose (mg/kg)	Route
Blockade by reserpine pretreatment of amantadine-induced transient increase in myocardial contractile force	dog	1 to 3	intravenous
Potentiation of norepinephrine vasopressor response	dog	40.5	intravenous
Block of phenethylamine vasopressor response	dog	≥13.5	intravenous
Block of norepinephrine uptake into the heart	mouse	≥31	intraperitoneal

Amantadine hydrochloride is well absorbed by the oral route in all species studied; the rate of excretion of the drug is first order. The metabolism of amantadine hydrochloride in the monkey and mouse is somewhat similar to that in man. The monkey and mouse metabolize the drug less than the rat, dog and rabbit. The urine appears to be the major route of elimination. The dog has been shown to convert a portion of the administered drug to its N-methyl derivative excreted in the urine. No other metabolites have been identified.

TOXICOLOGY

The results of acute oral, intraperitoneal and intravenous toxicity studies in several species of laboratory animals are shown in the following table.

Acute Toxicity of Amantadine Hydrochloride
LD_{50} (95% confidence limits)

Species	Sex	Oral (mg/kg)	Intraperitoneal (mg/kg)	Intravenous (mg/kg)
Mouse	F	700 (621, 779)	205 (194, 216)	97 (88,106)
Rat	F	890 (761, 1019)	223 (167, 279)	
Rat	M	1275 (1095, 1455)		
Rat, neonatal	M,F		150 (111,189)	
Guinea Pig	F	360 (316, 404)		
Dog	M,F	>372[a]		
Monkey, rhesus	M	>500[a]		>37

[a] Emesis occurred

Oral LD_{50} values for dogs and rhesus monkeys could not be obtained because the animals vomited. One dog, which did not vomit, died at 93 mg/kg following signs of central nervous system stimulation, including clonic convulsions. In monkeys at doses of 200-500 mg/kg, emesis always occurred and convulsions appeared irregularly. At levels near the LD_{50}, signs of central nervous system stimulation followed by tremors and brief clonic convulsions were common to the three rodent species by all routes of administration. All deaths occurred promptly, usually within a few minutes, or at the most within a few hours after compound administration.

Chronic oral toxicity experiments were carried out with rats (88-94 weeks), dogs (2 years) and monkeys (6 months). The amantadine hydrochloride dose levels were 16, 80 and 100-160 mg/kg; 8, 40 and 40-80 mg/kg; and 10, 40 and 100 mg/kg, respectively, administered daily (5 days per week). In rats, at the high dose only, a statistically significant decrease in body weight and excess mortality was seen; signs of central nervous system stimulation after each dosing, reduced food intake, and susceptibility to infection were noted. In dogs, tremors, hyperexcitability and emesis were seen at the mid- and high-dose levels, and food intake was reduced. One dog in the mid-, and three dogs in the high-dose group died. In an additional study in the dog, 30 mg/kg of amantadine hydrochloride, divided into two doses six hours apart, was given seven days per week for six months. No drug-related effects were seen. In the

monkey study, stimulation was continuously evident at the high-dose level but was seen only sporadically in the mid-dose group. No other effects were noted. There were no amantadine-related pathological or histomorphological changes seen in any of these studies conducted in rats, dogs and monkeys.
To study compatibility of amantadine hydrochloride with other types of drugs used for the treatment of Parkinson's syndrome, acute oral toxicity experiments in mice and subacute oral toxicity studies of rats and monkeys were carried out. In mice, high doses of oral levodopa, 200 and 400 mg/kg, decreased the acute intraperitoneal LD_{50} of amantadine hydrochloride by 10% and 16% respectively. Atropine, in oral doses of 4 and 40 mg/kg had no effect on the acute intraperitoneal LD_{50} of amantadine hydrochloride in mice.

In rats and monkeys, there was little or no interaction or incompatibility when amantadine hydrochloride was administered daily and concurrently with levodopa or atropine for 3 months. In rats, levodopa, 100 to 400 mg/kg alone or combined with amantadine hydrochloride 10 or 30 mg/kg, was well tolerated with only urine and saliva discoloration typical of levodopa. When atropine, 5 to 100 mg/kg was tested together with amantadine hydrochloride, 30 mg/kg, the only adverse finding was slightly decreased weight gain and food consumption. In monkeys, levodopa, 50 to 1000 mg/kg alone or combined with amantadine hydrochloride 10 or 30 mg/kg caused only urine discoloration and, at the highest doses, some abrupt (involuntary) jerky movements, seen occasionally also in untreated rhesus monkeys. Atropine at 0.05 to 30 mg/kg alone or combined with amantadine hydrochloride 30 mg/kg caused only pupil dilatation and dryness of the mouth.

Effects on Reproduction

In rats, a 3-litter reproduction study was performed. Amantadine hydrochloride 10 mg/kg in the diet, resulted in no observed abnormality. When the dose was raised to 32 mg/kg, fertility and lactation indices were somewhat depressed. No fetal abnormalities were noted in this study.

In a different study, virgin rats were dosed orally with amantadine hydrochloride (50 or 100 mg/kg) from 5 days prior to mating until day 6 of pregnancy. Autopsy performed on day 14 of gestation showed significant decreases in the number of implantations and number of resorptions at 100 mg/kg. Teratology studies were performed in rats by administering the drug (37, 50 or 100 mg/kg) orally on days 7-14 of gestation. Autopsy just before parturition showed increases in resorption and decreases in the number of pups per litter at 50 and 100 mg/kg. Malformation of pups occurred with a frequency of 0% at the 37 mg/kg, 4.7% at the 50 mg/kg and 17% at the 100 mg/kg level. The majority of changes were skeletal (mainly spinal column and rib deficits), but some visceral changes (edema, undescended ovaries and testes) were also noted.

In a teratology study carried out in Japan, pregnant rats received amantadine hydrochloride (40 or 120 mg/kg) orally on days 9 to 14 of gestation. At the higher dose, the dams had a slightly decreased rate of increase in body weight, the fetal mortality rates were increased and the surviving pups showed decreased body weight. The difference, however, disappeared after the end of the first postnatal week. There were no malformations or skeletal abnormalities.

In a teratogenic study mice received amantadine hydrochloride 10 or 40 mg/kg, p.o., from the 7th to the 12th day of pregnancy. The most important findings included, at the high dose level, increased fetal mortality and reduced body weight of the dams as well as of the surviving offspring. One case of exencephalia was found in the high-dose group which, in the opinion of the investigators, was not drug-related.

Rabbits were mated and dosed six days later with 8 or 32 mg/kg through day 16 and sacrificed on day 28. In a separate study, rabbits received amantadine hydrochloride orally, 100 mg/kg on days 7 to 14 of gestation. No teratogenic or other adverse effects were seen in these rabbit studies.

Carcinogenesis and Mutagenesis

No long-term studies have been performed to evaluate the carcinogenic potential of amantadine hydrochloride. The mutagenic potential of the drug has not yet been determined in experimental systems.

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B. PRECLINICAL

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IMPORTANT: PLEASE READ

PrENDANTADINE
(amantadine hydrochloride) capsules, USP

This leaflet is a summary and will not tell you everything about ENDANTADINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ENDANTADINE is used to relieve the symptoms of Parkinson's disease as well as conditions similar to those of Parkinson's disease.

What it does:

How Parkinson's disease occurs is still unknown, but the result of having it is a reduction in the amount of a chemical messenger in the brain known as dopamine; this lack of dopamine causes the symptoms of Parkinsonism such as loss of muscle control and stiffness. ENDANTADINE is believed to reduce these symptoms by increasing the amount of dopamine in the brain.

When it should not be used:

ENDANTADINE should not be used in patients with known sensitivity to amantadine or to any components of the formulation (see "What the Important Nonmedicinal Ingredients are").

What the medicinal ingredient is:

Amantadine hydrochloride

What the important non-medicinal ingredients are:

Fill material: Hydrogenated vegetable oil, lecithin unbleached, soya bean oil, vegetable shortening, and yellow wax

Shell material: FD&C Red # 40, gelatine, glycerine, methyl paraben, propyl paraben, titanium dioxide, white marking ink opacode, s-1-7077.

What dosage forms it comes in:

Capsules: Each red soft gelatin capsule contains 100 mg of amantadine hydrochloride. Bottles of 100 capsules

WARNINGS AND PRECAUTIONS

Important information to know about ENDANTADINE

- A small number of suicidal attempts, some of which have been fatal, have been reported in patients treated with ENDANTADINE.
- If your disease improves on ENDANTADINE, resume normal activities gradually and cautiously. Be careful not to overdo physical activity.
- ENDANTADINE can cause dizziness or blurred vision. Make sure you know how you react to this medication before driving, operating machinery or doing any work requiring alertness and adequate motor coordination.
- You should not stop ENDANTADINE suddenly as your condition may deteriorate.
- An uncommon but life-threatening condition of Neuroleptic Malignant Syndrome has occurred with dose reduction or withdrawal of ENDANTADINE therapy. Neuroleptic Malignant Syndrome is characterised by fever or hyperthermia; neurologic findings including muscle rigidity, involuntary movements, altered consciousness; and other disturbances such as autonomic dysfunction, tachycardia, tachypnea, hyper- or hypotension; laboratory findings such as creatinine phosphokinase elevation, leukocytosis, and increased serum myoglobin.
- Patients with Parkinson's disease have a higher risk of developing a type of skin cancer "melanoma" than the general population. Your doctor may ask you to undergo periodic dermatologic testing.

Studies of people with Parkinson's disease show that they may be at an increased risk of developing melanoma (a form of skin cancer) when compared to people without Parkinson's disease. It is not know if this problem is associated with Parkinson's disease or the drugs used to treat Parkinson's disease. ENDATADINE is one of the drugs used to treat Parkinson's disease therefore, patients treated with ENDANTADINE should have periodic skin examinations.

BEFORE taking ENDANTADINE you should tell your doctor if:

- You are allergic to amantadine or any other drugs.
- You are taking any other medications including over the counter medicines, vitamins, supplements or herbal products.
- You have epilepsy or any other type of seizures since ENDANTADINE may increase seizure activity.
- You have a history of psychiatric disorders or substance abuse since ENDANTADINE can worsen mental problems.
- You are 65 years of age or older and/or have kidney problems, as your doctor may reduce your dose of ENDANTADINE.

- You ever had heart problems, swelling in your extremities or low blood pressure on standing you doctor may need to adjust your dose ENDANTADINE.
- You have liver disease or recurring skin rash.
- You are pregnant or plannimg to become pregnant.
- You are breast-feeding.
- Your child is less than 1 year old and taking this medicine.

INTERACTIONS WITH THIS MEDICATION

Make sure you talk to your doctor about any other conditions you may have and all other medications you are taking, including prescription, non-prescription and herbal and/or natural products.

Concurrent use of amantadine and anticholinergic drugs may cause atropine-like effects and require a reduction in the dose of ENDANTADINE or the anticholinergic drug.

PROPER USE OF THIS MEDICATION

Usual dose:

- Parkinson's syndrome: The usual dose of ENDANTADINE is 100 mg twice daily. If you are receiving ENDANTADINE with levodopa, your doctor may adjust the dose of ENDANTADINE to 100 mg once a day or 100 mg twice a day while the dose of levodopa is being increased. In some cases, your doctor may increase your dose of ENDANTADINE to 300 mg per day in divided doses.
- Drug-Induced Extrapyramidal Symptoms: The usual dose of ENDANTADINE is 100 mg twice daily. Your doctor may adjust the dose if you do not respond to ENDANTADINE effectively.
- Impaired Renal Function: If you have kidney problems, a lower dose or alternating daily doses may be used. Your doctor will decide what the best dose is for you.

Overdose:
If you think you may have taken more ENDANTADINE than you should, talk to your doctor immediately or contact the Emergency room of the nearest hospital.

Missed Dose:
It you miss a dose of this medicine, check with your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with their needed effects, medicines like ENDANTADINE can sometimes cause unwanted effects and some of them are serious. You should report any unusual symptoms to your doctor.

The more common side effects with ENDANTADINE are nausea, dizziness (light headedness), insomnia, and blurred vision. The less common side effects are depression, anxiety and irritability, swelling of the hands, legs, or feet, difficulty urination, shortness of breath, skin rash, and suicidal ideation.

SERIOUS 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	
Uncommon	Suicidal attempt, thoughts of suicide, depression, hallucinations, confusion, instances of seizures		✓	
	Fever muscle rigidity, high or low blood pressure, fast heart rate		✓	
Rare	muscle pain		✓	

This is not a complete list of side effects. For any unexpected effects while taking ENDANTADINE, contact your doctor or pharmacist.

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HOW TO STORE IT

Store at controlled room temperature (15° to 30° C) in a tightly closed container.

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 can be obtained by contacting the sponsor, Bristol Myers Squibb Canada, at: 1-866-463-6267

This leaflet was prepared by Bristol Myers Squibb Canada

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