PRODUCT MONOGRAPH

MYLAN-AMANTADINE

(Amantadine Hydrochloride Capsules, USP)

Capsules - 100 mg

Antiviral Agent

Mylan Pharmaceuticals ULC
85 Advance Road.
Etobicoke, ON
M8Z 2S6

Date of Preparation:
June 9, 2009
Date of Revision:

Control#: 130467

PRODUCT MONOGRAPH

MYLAN-AMANTADINE

(Amantadine Hydrochloride Capsules, USP)

Capsules - 100 mg

THERAPEUTIC CLASSIFICATION

Antiviral Agent

ACTIONS AND CLINICAL PHARMACOLOGY

The antiviral activity of MYLAN-AMANTADINE (amantadine HCl) against influenza A virus in humans is not completely understood. The mode of action of MYLAN-AMANTADINE appears to be the prevention of the release of infectious viral nucleic acid into the host cell.

In man, amantadine HCl is well 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. Half-life values have ranged from 9 to 37 hours, with an average of 24 hours.

A comparative bioavailability study was performed using normal human volunteers. The rate and extent of absorption after a single oral dose of MYLAN-AMANTADINE 100 mg or 100 mg of a marketed Canadian brand product was measured and compared. The results can be summarized as follows:

Mean Pharmacokinetic Data

Parameter	Test	Geometric Mean Arithmetic Mean (C.V.) Reference	Ratio of Means
AUC_T (ng.h/mL)	4316 4429 (23.3)	4359 4436 (20.9)	0.99
AUC_I (ng.h/mL)	4675 4785 (23.5)	4722 4819 (20.9)	0.99
C_{max} (ng/mL)	224 226 (16.2)	226 229 (15.4)	0.99
T_{max}* (h)	2.29 (0.724)	2.63 (0.912)	--
$T_{½}$* (h)	14.6 (4.25)	14.6 (4.01)	--

*For the T_{max} and $T_{½}$ parameters these are the arithmetic means (standard deviation).

INDICATIONS AND CLINICAL USE

Influenza A virus respiratory infections

MYLAN-AMANTADINE (amantadine HCl) is indicated in the prevention (prophylaxis) and treatment of respiratory infections caused by influenza A virus strains. MYLAN-AMANTADINE should be considered especially for high risk patients, close household or hospital ward contacts of index cases and patients with severe influenza A virus infections. Because amantadine HCl does not appear to suppress antibody response, it can be used chemoprophylactically in conjunction with inactivated influenza A virus vaccine until protective antibody responses develop. There is no clinical evidence that this drug has efficacy in the

prophylaxis or treatment of viral respiratory infections other than those caused by influenza A virus strains.

MYLAN-AMANTADINE provides antiviral activity against influenza A virus infections both when administered prophylactically and therapeutically.

CONTRAINDICATIONS

MYLAN-AMANTADINE (amantadine HCl) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Patients with a history of epilepsy or other "seizures" should be observed closely for possible untoward central nervous system effects.

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.

Use In Pregnancy

Safety of use in pregnancy has not been established. Therefore, MYLAN-AMANTADINE (amantadine HCl) should not be used in women of 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).

Since the drug is secreted in the milk, MYLAN-AMANTADINE should not be administered to nursing mothers.

PRECAUTIONS

General

The dose of MYLAN-AMANTADINE (amantadine HCl) may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema or ortho-static hypotension. Since amantadine HCl is not metabolized and is mainly excreted in the urine, it may accumulate when renal function is inadequate.

Patients receiving MYLAN-AMANTADINE who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness is important.

Patients with Special Diseases and Conditions

Care should be exercised when administering MYLAN-AMANTADINE to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents.

Drug Interaction

Careful observation is required when MYLAN-AMANTADINE is administered concurrently with central nervous system stimulants.

ADVERSE REACTIONS

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

The more important adverse reactions are orthostatic hypotensive episodes, congestive heart failure, depression, psychosis and urinary retention; and rarely convulsions, reversible leukopenia and neutropenia, and abnormal liver function test results.

Other adverse reactions of less importance which have been observed are: anorexia, anxiety, ataxia, confusion, hallucinations, constipation, dizziness (light- headedness), dry mouth, headache, insomnia, livedo reticularis, nausea, peripheral edema, drowsiness, dyspnea, fatigue, hyperkinesia, irritability, nightmares, rash, slurred speech, visual disturbance, vomiting and weakness; and very rarely eczematoid dermatitis and oculogyric episodes.

Some side effects were transient and disappeared even with continued administration of the drug.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Limited data are available concerning clinical effects and management of amantadine HCl overdosage. An elderly patient with Parkinson's syndrome who took an overdose of 2.8 g of amantadine hydrochloride in a suicide 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 behaviour. Convulsions did not occur, possibly because the patient had been receiving phenytoin prior to the acute ingestion of amantadine HCl.

There is no specific antidote. 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. The pH of the urine has been reported to influence the excretion rate of amantadine hydro-chloride. 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

Dosage for Prophylaxis and Treatment of Influenza A Respiratory Infections:

Adult: The adult daily dosage of MYLAN-AMANTADINE (amantadine HCl) is 200 mg: two 100 mg capsules as a single daily dose, or the daily dosage may be split into one capsule of 100 mg twice a day. If central nervous system effects develop on once-a-day dosage, a split dosage schedule may reduce such complaints.

Children: For children 9 yrs to 12 yrs of age, the total daily dose is 200 mg given as one capsule of 100 mg twice a day.

Impaired Renal Function: Depending upon creatinine clearance, the following dosage adjustments are recommended:

Creatinine Clearance ($mL/min/1.73m^2$)	Amantadine HCl Dosage
30-50	200 mg 1st day and 100 mg each day thereafter
15-29	200 mg 1st day followed by 100 mg on alternate days
<15	200 mg every 7 days

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

Prophylactic dosing should be started in anticipation of contact or as soon as possible after contact with individuals suffering from influenza A respiratory infection. MYLAN-AMANTADINE should be continued daily for at least 10 days following a known exposure, or up to 90 days in case of possible repeated and unknown exposure. Treatment of influenza A should be started as soon as possible after onset of symptoms and should be continued for 24 to 48 hours after the disappearance of symptoms.

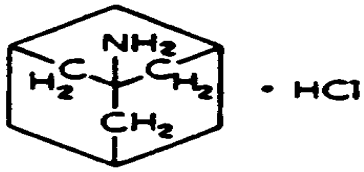
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Amantadine HCl, USP

Chemical Names: Tricyclo[3.3.1.$1^{3,7}$]decan-1-amine, hydrochloride;
1-Adamantanamine hydrochloride

Structural Formula:



Amantadine hydrochloride

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

Molecular Weight: 187.71

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

Composition

Each MYLAN-AMANTADINE (amantadine HCl) capsule contains

Active Ingredient:

100 mg of amantadine hydrochloride.

Excipients: Beeswax, D&C Red No. 33, Gelatin, Glycerin, Hydrogenated Soybean Flakes, Hydrogenated Vegetable Oil, Lecithin, Parabens, Refined Soybean Oil, Titanium Dioxide, Water.

Stability and Storage Recommendations

Store in a light resistant container at temperatures between 15 - 30°C.

AVAILABILITY OF DOSAGE FORMS

MYLAN-AMANTADINE (amantadine HCl) 100 mg Capsules are red, oblong, soft gelatin capsules imprinted in white ink: "**A100**" on one side, with off-white opaque semi-solid filling.

MYLAN-AMANTADINE (amantadine HCl) 100 mg Capsules are available in bottles of 100 and 500.

PHARMACOLOGY

Animal Studies:

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 HCl causes norepinephrine release and blockade of norepinephrine re-uptake at peripheral autonomic neuron storage sites.

RESPONSE	Species	Amantadine Dose (mg/kg)	Route
Blockade by reserpine pre-treatment of amantadine-induced transient increase in myocardial contractile force.	dog	1 to 3	intravenous
Potentiation of norepine-phrine 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 which is 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 Table 1. 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.

TABLE 1 ACUTE TOXICITY OF AMANTADINE HYDROCHLORIDE
LD_{50} (95% confidence limits)

SPECIES	SEX	ORAL (mg/kg)	INTRAPERITIONEAL (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*		
Monkey, rhesus	M	> 500*		>37

* Emesis occurred

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 middle and high levels, and food intake was reduced. One dog in the middle, and three dogs in the high-level group died. In an additional dog experiment, 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 experiment, stimulation was continuously evident in the high level and was seen sporadically in the middle-level group. No other effects were noted. In none of these experiments with rats, dogs and monkeys were any amantadine hydrochloride-related pathological or histomorpho-logical changes seen.

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 experiment.

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 mentioned.

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 mortality rate of the fetus was increased and the surviving pups showed decreased body weight. This difference, however, disappeared after the end of the first postnatal week. There were no malformations or skeletal abnormalities.

In a teratogenetic 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 include, at the high dose level, increased fetus mortality and reduced body weight of the dams as well as of the surviving offspring. One case of exencephalia was found in the high-level 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. A separate study was reported in which 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 experiments.

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Antiparkinsonian Agent

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THERAPEUTIC CLASSIFICATION

Antiparkinsonian Agent

ACTION AND CLINICAL PHARMACOLOGY

While the mechanism of action of MYLAN-AMANTADINE (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 amantadine HCl 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, amantadine HCl 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.

A comparative bioavailability study was performed using normal human volunteers. The rate and extent of absorption after a single oral dose of MYLAN-AMANTADINE 100 mg or 100

mg of a marketed Canadian brand product was measured and compared. The results can be summarized as follows:

Mean Pharmacokinetic Data

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AUC_I (ng.h/mL)	4675 4785 (23.5)	4722 4819 (20.9)	0.99
C_{max} (ng/mL)	224 226 (16.2)	226 229 (15.4)	0.99
T_{max}* (h)	2.29 (0.724)	2.63 (0.912)	--
$T_{1/2}$* (h)	14.6 (4.25)	14.6 (4.01)	--

*For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation)

INDICATIONS AND CLINICAL USE

MYLAN-AMANTADINE (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, amantadine hydrochloride has been used alone and in combination with anticholinergic antiparkinsonian drugs and with levodopa. The final therapeutic benefit seen with amantadine HCl is significantly less than that seen with levodopa. The maximal therapeutic benefit to be obtained with amantadine HCl is usually seen within one week. However, initial benefits may diminish with continued dosing.

MYLAN-AMANTADINE 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 MYLAN-AMANTADINE may result in better control of Parkinson's syndrome and may help to smooth out fluctuations in performance.

The comparative efficacy of MYLAN-AMANTADINE and anticholinergic antiparkinsonian drugs has not yet been established. When MYLAN-AMANTADINE 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.

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

Although anticholinergic-type side effects have been noted with amantadine HCl 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, MYLAN-AMANTADINE 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. MYLAN-AMANTADINE should be withdrawn after a period of time to determine whether there is recrudescence of extrapyramidal symptoms.

CONTRAINDICATIONS

MYLAN-AMANTADINE (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 HCl. 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. MYLAN-AMANTADINE (amantadine HCl) 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 MYLAN-AMANTADINE 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 HCl.

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

Patients receiving MYLAN-AMANTADINE 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

MYLAN-AMANTADINE (amantadine HCl) should not be discontinued abruptly since a few patients with Parkinson's syndrome experienced a parkinsonian crisis, i.e., sudden marked clinical deterioration, when this medication was suddenly stopped.

Neuroleptic Malignant Syndrome

Sporadic cases of possible Neuroleptic Malignant Syndrome (NMS) have been reported in association with dose reduction or withdrawal of amantadine HCl therapy. NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia; 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 MYLAN-AMANTADINE 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 MYLAN-AMANTADINE 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 MYLAN-AMANTADINE may need careful adjustment in patients with congestive heart failure, peripheral edema or orthostatic hypotension.

Care should be exercised when administering MYLAN-AMANTADINE 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 HCl, though a specific relationship between the drug and such changes has not been established.

Use in Pregnancy

Amantadine HCl 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, MYLAN-AMANTADINE should not be used in women of 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 MYLAN-AMANTADINE is not recommended in nursing mothers.

Pediatric Use

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

Drug interactions

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

Careful observation is required when MYLAN-AMANTADINE is administered concurrently with central nervous system stimulants.

ADVERSE REACTIONS

Adverse reactions reported below have occurred in patients while receiving amantadine hydrochloride alone or in combination with anti-cholinergic antiparkinson 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 HCl 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 behaviour (Vol 3:85). Convulsions did not occur, possibly because the patient had been receiving phenytoin prior to the acute ingestion of amantadine HCl.

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 HCl. 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 amantadine HCl. Since the excretion rate of amantadine HCl 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 MYLAN-AMANTADINE (amantadine hydrochloride) is 100 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily. When MYLAN-AMANTADINE and levodopa are initiated concurrently, MYLAN-AMANTADINE 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 MYLAN-AMANTADINE is 100 mg twice a day.

Patients whose responses are not optimal with MYLAN-AMANTADINE 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 Symptoms:

The usual dose of MYLAN-AMANTADINE is 100 mg twice **a** day. Occasionally, patients whose responses are not optimal with MYLAN-AMANTADINE 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 Report, May 29, 1992.

Creatinine Clearance (mL/min/l.73 m^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.

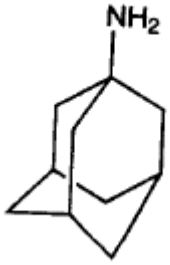
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Amantadine HC1, USP

Chemical Names: Tricyclo[3 .3.1.1^{3,7}] decan-1-amine, hydrochloride;
1 -Adamantanamine hydrochloride

Structural Formula:



Amantadine hydrochloride

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

Molecular Weight: 187.71

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

Composition

Each MYLAN-AMANTADINE (amantadine HCl) capsule contains

Active Ingredient:

100 mg of amantadine hydrochloride.

Excipients: Beeswax, D&C Red No. 33, Gelatin, Glycerin, Hydrogenated Soybean Flakes, Hydrogenated Vegetable Oil, Lecithin, Parabens, Refined Soybean Oil, Titanium Dioxide, Water.

Stability and Storage Recommendations

Store in a light resistant container at temperatures between 15 – 30°C.

AVAILABILITY OF DOSAGE FORMS

MYLAN-AMANTADINE (amantadine HCl) 100 mg Capsules are red, oblong, soft gelatin capsule imprinted in white ink: **"A100"** on one side with off-white opaque semisolid filling.

MYLAN-AMANTADINE (amantadine HCl) 100 mg Capsules are available in bottles of 100 and 500.

PHARMACOLOGY

The available evidence from animal experiments points to an interaction with dopamine and perhaps with other catecholamines within the brain as the major mode of action of MYLAN-AMANTADINE (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 ant icholinergic 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 HCl caused several pharmacologic effects at relatively high doses. Signs of motor activity stimulation (increased spontaneous motor activity and antagonism of tetrabenazjne-jnduced 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 HCl causes norepinephrine release and blockade of norepinephrine re-uptake at peripheral autonomic neuron storage sites.

Response	Species	Amantadine HCl 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	intra venous
Block of norepinephrine uptake into the heart	mouse	≥31	intra-peritoneal

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, intrapenitoneal 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)**	**Intra-peritoneal (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 middle-dose group. No other effects were noted. There were no amantadine-related pathological or histomor-phological changes seen in any of these studies con-ducted 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 in rats and monkeys were carried out. In mice, high doses of oral levodopa, 200 and 400 mg/kg, decreased the acute intrapenitoneal LD_{50} of amantadine HCl by 10% and 16%, respectively. Atropine, in oral doses of 4 and 40 mg/kg had no effect on the acute intrapenitoneal 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 partunition 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. This 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 HCl. The mutagenic potential of the drug has not yet been determined in experimental systems.

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