PRODUCT MONOGRAPH

phl-AMANTADINE
(Amantadine Hydrochloride Capsules, USP)
100 mg

phl-AMANTADINE SYRUP
(Amantadine Hydrochloride Syrup, USP)
10 mg/mL

Antiparkinsonian Agent

Pharmel Inc.
8699 8th Avenue
Montreal (Quebec)
H1Z 2X4

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THERAPEUTIC CLASSIFICATION

Antiparkinsonian Agent

ACTION AND CLINICAL PHARMACOLOGY

The exact mechanism of action of amantadine hydrochloride in the treatment of parkinsonism and drug-induced extrapyramidal reactions is not known but appears to be unrelated to its activity in the prophylaxis and symptomatic treatment of influenza A virus infections.

Amantadine hydrochloride does not have any appreciable anticholinergic activity; the drug probably exerts a potentiating effect on catecholaminergic, including dopaminergic, neurotransmission in the CNS.

Amantadine hydrochloride is readily absorbed from the GI tract, is not metabolized and is excreted unchanged in the urine by glomerular filtration and tubular secretion

Amantadine hydrochloride 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.

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

Compared with otherwise healthy adult individuals, the clearance of amantadine hydrochloride 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 hydrochloride 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 related factors is not known.

A comparative bioavailability study was performed using normal human volunteers. The rate and extent of absorption after a single 100 mg dose of Symmetrel and phl-AMANTADINE was measured and compared. The results can be summarized as follows:

	(1) Symmetrel 100 mg	(2) phl-AMANTADINE 100 mg	Ratio (2)/(1)
AUC (ng.h/mL)	5268.3	5315.2	1.01
Cmax (ng/ml)	258.1	252.2	0.98
Tmax (h)	3.7	3.75	1.01
T ½ (h)	14.06	13.27	0.94

INDICATIONS AND CLINICAL USE

PARKINSON'S SYNDROME AND DRUG INDUCED EXTRAPYRAMIDAL REACTIONS:

Amantadine hydrochloride is useful in the treatment of Parkinson's Syndrome and in the short term management of drug-induced extrapyramidal symptoms.

Clinical Use:

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

Amantadine hydrochloride 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 amantadine hydrochloride may result in better control of Parkinson's syndrome and may help to smooth out fluctuations in performance.

The comparative efficacy of amantadine hydrochloride and anticholinergic antiparkinson drugs has not yet been established. When amantadine hydrochloride or anticholinergic antiparkinson 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.

Amantadine hydrochloride is effective in decreasing the severity or eliminating drug-induced extrapyramidal reactions including parkinsonism syndrome, akathisia and dystonia. It is not effective in the treatment of tardive dyskinesia.

Anticholinergic-type side effects have been noted with amantadine hydrochloride when used in patients with drug-induced extrapyramidal reactions, however, the incidence of these side effects is lower than that observed with anticholinergic antiparkinson drugs.

Although antiparkinsonian agents should not usually be used prophylactically during neuroleptic administration, they may be given when needed to suppress extrapyramidal symptoms. As such, amantadine hydrochloride 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. Amantadine hydrochloride should be discontinued after a period of time to determine whether there is a recurrence of extrapyramidal symptoms.

CONTRAINDICATIONS

phl-AMANTADINE (Amantadine hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

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

Patients with a history of epilepsy or other seizures should be observed closely as amantadine hydrochloride may cause increased seizure activity.

Pregnancy: Safe use of amantadine hydrochloride during pregnancy has not been established. There are no adequate and well controlled studies in pregnant women. The drug should be used during pregnancy only when the potential benefits outweigh the possible risks to the fetus (see **TOXICOLOGY**).

Lactation: Amantadine hydrochloride is excreted into breast milk. Amantadine hydrochloride should not be administered to nursing mothers.

Pediatric Use: The safety and efficacy of amantadine hydrochloride in newborn infants and infants below the age of 1 year have not been established.

PRECAUTIONS

General: Amantadine hydrochloride should not be discontinued abruptly since a few patients with Parkinson's disease have experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration when this medication was suddenly stopped. The dose of anticholinergic drugs or of amantadine hydrochloride should be reduced if atropine-like effects appear when these drugs are used concurrently.

Use in Elderly: Because amantadine hydrochloride is not metabolized and is mainly excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of amantadine hydrochloride should be reduced in patients with renal impairment and in individuals who are 65 years of age or older.

Patients with Special Diseases and Conditions: The dose of amantadine hydrochloride may need careful adjustment in patients with congestive heart failure, peripheral edema, or orthostatic hypotension.

Care should be exercised when administering amantadine hydrochloride to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when amantadine hydrochloride is administered concurrently with central nervous system stimulants.

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

Occupational hazards: Patients receiving amantadine hydrochloride who note CNS effects or blurring of vision should be cautioned against driving or working in situations where alertness is important.

ADVERSE REACTIONS

The following adverse affects have occurred in patients while receiving amantadine hydrochloride alone or in combination with anticholinergic antiparkinsonian 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 functions tests.

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

Less frequently (1-5%) reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension and headache.

Infrequently (0.1-1%) occurring adverse reactions are: congestive heart failure, psychosis, urinary retention, dyspnea, fatigue, skin rash, vomiting, weakness, slurred speech and visual disturbance. Rarely (less than 0.1%) occurring adverse reactions are: instances of convulsion, leukopenia, neutropenia, eczematoid dermatitis and oculogyric episodes.

Some adverse effects were transient and disappeared often with continued administration of the drug.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms:

Overdosage has been characterized in one elderly patient who ingested 2.8 g of amantadine hydrochloride . The patient had slightly dilated pupils which contracted minimally to light, urinary retention, mild, mixed acid-base disturbances and an acute toxic psychosis manifested as disorientation, confusion, visual hallucinations, and aggressive behavior. Convulsions did not occur, possibly because the patient had been receiving phenytoin prior to acute ingestion of amantadine hydrochloride .

Treatment:

There is no specific antidote. However, slowly administered intravenous physostigmine in 1 and 2 mg doses in an adult at 1 to 2 hours intervals and 0.5 mg doses in a child at 5 to 10 minute intervals 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; 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.

Since the excretion rate of amantadine hydrochloride increases rapidly when the urine is acidic, the administration of urine acidifying drugs 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 hyperactivity and convulsions; if required, sedation and anticonvulsant therapy should be administered. The patient should be observed for the possible development of arrhythmias and hypotension; if required, appropriate antiarrhythmic and antihypotensive therapy should be given.

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 Parkinsonism:

Adult: The usual dose of phl-AMANTADINE (amantadine hydrochloride) is 100 mg twice a day when used alone. Amantadine hydrochloride has an onset of action usually within 48 hours.

The initial dose of phl-AMANTADINE 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, if necessary.

Occasionally, patients whose responses are not optimal with phl-AMANTADINE at 300 mg daily may benefit from an increase up to 400 mg daily in divided doses. However such patients should be supervised closely by their physicians.

Patients initially deriving benefit from phl-AMANTADINE not uncommonly experience a fall-off of effectiveness after a few months. Benefit may be regained by increasing the dose to 300 mg daily. Alternatively, temporary discontinuation of phl-AMANTADINE for several weeks, followed by reinitiation of the drug, may result in regaining benefit in some patients. A decision to use other antiparkinson drugs may be necessary.

Dosage for Concomitant Therapy:

Some patients who do not respond to anticholinergic antiparkinson drugs may respond to phl-AMANTADINE. When phl-AMANTADINE or anticholinergic antiparkinson drugs are each used with marginal benefit, concomitant use may produce additional benefit.

When phl-AMANTADINE and levodopa are initiated concurrently, the patient can exhibit rapid therapeutic benefits. phl-AMANTADINE should be held constant at 100 mg daily or twice daily while the daily dose of levodopa is gradually increased to optimal benefit.

When phl-AMANTADINE is added to optimal well-tolerated doses of levodopa, additional benefit may result, including smoothing out the fluctuations in improvement which sometimes occur in patients on levodopa alone. Patients who require a reduction in their usual dose of levodopa because of development of side effects may possibly regain lost benefit with the addition of phl-AMANTADINE.

Dosage for Drug-Induced Extrapyramidal Reactions:

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

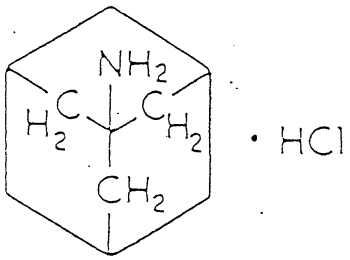
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Amantadine Hydrochloride

Chemical Name: 1-adamantanamine hydrochloride.

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



Molecular Weight: 187.72

Description: Amantadine hydrochloride is a stable /white or nearly white crystalline powder which has a bitter taste and is freely soluble in water and soluble in alcohol.

Stability and Storage Recommendations:

Storage: Store at controlled room temperature (15˚-30˚C).

AVAILABILITY OF DOSAGE FORMS

Capsules: Each red soft gelatin capsule imprinted with "0100" on one side and " Amant " on the other contains 100 mg of amantadine hydrochloride , USP. Bottles of 100 and 1000. Tartrazine free.

Syrup: Each 5 mL of clear colorless syrup contains 50 mg of amantadine hydrochloride, USP. Also contains parabens. Tartrazine free. Bottles of 250 mL and 500 mL.

PHARMACOLOGY

The exact mechanism of action of amantadine hydrochloride in the treatment of parkinsonism and drug-induced extrapyramidal reactions is not known but appears to be unrelated to its activity in the prophylaxis and symptomatic treatment of influenza A virus infections. Amantadine hydrochloride does not have any appreciable anticholinergic activity; the drug probably exerts a potentiating effect on catecholaminergic, including dopaminergic, neurotransmission in the CNS. In one study, amantadine hydrochloride Hydrochloride given IV to dogs reportedly caused release of catecholamines from peripheral nerve storage sites; a similar mechanism for the drug's central activity was proposed.

It has been postulated that amantadine hydrochloride causes release of dopamine from synaptosomes; however, this may occur only following doses higher than those employed clinically.

There is some evidence that Amantadine, in usual therapeutic concentrations, may exert its antiparkinsonism activity by blocking the reuptake of dopamine into presynaptic neurons, thus causing accumulation of dopamine in the presynaptic clefts of dopaminergic neurons in the basal ganglia. In addition, the drug may cause direct stimulation of postsynaptic receptors.

In animals, several pharmacologic effects resulted from administration of amantadine hydrochloride at relatively high doses. In mice, oral doses of 35-40 mg/Kg and above produced signs of motor activity stimulation (increased spontaneous motor activity and antagonism of tetrabenazine-induced sedation) occurred.

In dogs, a transient vasodepressor effect, cardiac arrythmias and a weak ganglionic-blocking effect were observed following intravenous doses of 13.5 mg/Kg or above. In the rat and rabbit, EEG activation has been reported with high parenteral doses. In addition, relatively high doses of amantadine hydrochloride caused several effects in dog (potentiation of norepinephrine

vasopressor response; block of phenethylamine vasopressor response; increase in myocardial contractible force) and mouse (block of norepinephrine uptake into the heart; antagonism of tetrabenazine effects) indicative of a block of uptake of norepinephrine into labile stores.

Amantadine hydrochloride is well absorbed by the oral route in all species studied. The rate of excretion of the drug is first order. The monkey and the mouse appear to metabolize it less than other animals (rat, dog and rabbit) and most nearly approximate man. There is no evidence for metabolism of the drug in man. The major route of elimination is via urine.

Only the dog has been shown to convert a portion of the administered drug to its N-methylderivative which is excreted in the urine. No other metabolites have been identified.

TOXICOLOGY

Acute Toxicity: The acute toxicity of amantadine hydrochloride by the oral, intraperitoneal, and intravenous route of administration was determined in several species of laboratory animals and the results are presented in Table 1.

Table 1. Acute Toxicity of amantadine hydrochloride (48)

LD_{50} and 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]		>37
Monkey, rhesus,M	>500[a]		
Monkey, African green, F	>75		
Horse, M, F	>96		

[a] Some emesis occured.

The toxic signs produced by lethal or near-lethal doses of amantadine hydrochloride in these species were similar. Signs of central nervous system stimulation followed by tremors and brief clonic convulsions were common to the 3 rodent species by all routes of administration. Death was usually preceded by signs of respiratory distress and convulsions. In spite of repeated convulsions, surviving animals appeared to be normal.

All deaths in small animals occurred quite promptly. In mice after intravenous doses of amantadine hydrochloride , death occurred between 7 min. and 2 hours; intraperitoneal doses

caused deaths in 15 to 30 min; oral doses between 30 min. and 2 hours. In rats, death occurred 30 min. to 2 hours after intraperitoneal doses and 30 min. to 24 hours after oral doses. In guinea pigs oral doses of amantadine hydrochloride caused most deaths between 1 and 20 hours, with a single animal dying at 44 hours. In the dog, at 93 mg/Kg and above, 3 of 4 vomited and showed all the other signs of central nervous system stimulation, including clonic convulsions, varying in intensity possibly with the amount of drug lost with emesis. One dog, which did not vomit, died at 93mg/Kg.

In rhesus monkeys, amantadine hydrochloride orally caused no deaths at any dose tested and no signs at 80 mg/Kg or less.

Acute oral toxicity experiments in mice and subacute oral toxicity studies in rats and monkeys were carried out to study compatibility of amantadine hydrochloride with other types of drugs used for the treatment of Parkinson syndrome. In mice, high doses of oral levodopa, 200 and 400 mg/Kg, decreased the acute intraperitoneal LD50 of amantadine hydrochloride by 10 and 16%, respectively. Oral doses of Atropine 4 and 40 mg/Kg, had no effect on the acute intraperitoneal LD_{50} of amantadine hydrochloride in mice.

Chronic Toxicity:

Chronic oral toxicity experiments with amantadine hydrochloride were carried out with rats, dogs and monkeys.

Rats: Duration was 88-94 weeks with amantadine hydrochloride 16, 80, and 100-160 mg/Kg

administered daily 5 days per week. 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.

Dogs: Duration was 2 years and amantadine hydrochloride levels were 8, 40 and 40-80 mg/Kg administered daily 5 days per week. 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 of amantadine hydrochloride /Kg, divided into two doses six hours apart, was given seven days per week for six months. No drug-related effect was seen.

Monkeys: Duration was 6 months and amantadine hydrochloride levels were 10, 40 and 100 mg/Kg administered daily 5 days per week. 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-related pathological or histo-morphological changes seen.

REPRODUCTION STUDIES

Amantadine hydrochloride was administered orally in two separate doses of 120 mg/Kg (larger dose group) and 40 mg/Kg once a day for 6 successive days from the 9th to the 14 th day of pregnancy to nullipara rats of Wistar strain at the age of 3-4 months in order to examine its effects upon the foetus during the final stage of pregnancy and on their post-natal growth. The results indicated a slight retardation of increase in the body weight of dams in the larger dose group, but amantadine hydrochloride had no effect on the nidations at the end of the final stage of pregnancy.

In the larger dose group, however, the mortality rate of the foetus and the drop in body weight of surviving litter mates showed a significant difference from those of the control group, although no deformation was observed in the group. Finally, observations on the growth of the litter mates up to the end of the 6th post-natal week in the spontaneous parturition group indicated that the parturition rate was significantly lower in the larger amantadine hydrochloride dose group than in the control group. Amantadine hydrochloride at the doses tested had no effect on suckling rate, external differentiation, survival rate, auditory senses, mobility and development of gonadal functions or skeletal structure.

Holtzman rats and New Zealand white rabbits were dosed orally with amantadine hydrochloride (0,50,100 mg/Kg) for 5 days prior to mating until day 5 of pregnancy. In rats, but not in rabbits, results of autopsies performed in day 14 of gestation showed significant decreases in the number

of implantations and increases in the number of resorptions at 100 mg/Kg.

Teratology studies were performed in rats (0, 37,50 and 100 mg/Kg) by administering the drug orally on days 7-14 of gestation. Autopsy was just before expected parturition. Increases in resorption and decreases in the number of pups per litter were noted at 50 and 100 mg/Kg. Gross examination of rat pups at these dose levels revealed no malformation at 37 mg/Kg. Malformations at 50 and 100 mg/Kg included edema, malrotated hindlimbs, missing tail, stunting and brachygnatha. Examination of cleared and alizarin-stained skeletal preparations of foetuses revealed cases of absent ribs and absence of the lumbar and sacral portions of the spinal column in the 50 and 100 mg/Kg groups. Thus, in rats but not in rabbits, amantadine hydrochloride seems to be embryotoxic and teratogenic. Teratogenicity in rats occurs at 50 mg/Kg/day, or about 12 times the usual human dose.

In another study doses of 10 mg/Kg in the diet had no effect on rat reproduction or lactation or number of live births. At a dose of 32 mg/Kg, fertility and lactation indices were depressed.In another rabbit study three groups of virgin female New Zealand white rabbits were dosed orally with 0.8 or 32 mg/Kg of amantadine hydrochloride from day 6 after mating through and including day 16. After 28 days the uterine contents were exposed. Amantadine hydrochloride did not alter the parameters of pregnancy or the observed characteristics of the offspring. The conception rate and incidence of resorption was similar for all groups. Litter weight and fetal loss were unaffected. Total weight and fetal loss were unaffected. Fetal weight was not significantly reduced by either dose of the drug.

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PRODUCT MONOGRAPH

phl-AMANTADINE
(Amantadine Hydrochloride Capsules, USP)
100 mg

phl-AMANTADINE SYRUP
(Amantadine Hydrochloride Syrup, USP)
10 mg/mL

Antiviral Agent

Pharmel Inc.
8699 8th Avenue
Montreal, Canada
H1Z 2X4

Date of Preparation:
December 14, 2004
Date of Revision:

Control # : 095683, 095747

PRODUCT MONOGRAPH

phl-AMANTADINE

(Amantadine Hydrochloride Capsules, USP)

100 mg

phl-AMANTADINE SYRUP

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10 mg/mL

THERAPEUTIC CLASSIFICATION

Antiviral Agent

ACTION AND CLINICAL PHARMACOLOGY

The exact mechanism of the antiviral activity of amantadine hydrochloride has not been fully elucidated. The drug appears to produce a virostatic effect by inhibiting either the initiation of infection or virus assembly, thus reducing the possibility of viral replication and aborting clinical infection. To prevent infection, the drug must be present in the tissues prior to exposure to the virus; however, symptoms of influenza may be less severe and disappear more rapidly if the drug is given within 24 hours after the emergence of symptoms.

Reports are conflicting as to whether or not amantadine hydrochloride interferes with antibody formation in response to influenza A virus infection: a lowered antibody response may reflect amantadine amantadine hydrochloride's antiviral effect which reduces the amount of influenza virus produced. Amantadine hydrochloride does not appear to interfere with the immunogenicity of inactivated A virus vaccine.

Amantadine hydrochloride is readily absorbed from the GI tract, is not metabolized and is excreted unchanged in the urine by glomerular filtration and tubular secretion.

Amantadine hydrochloride 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.

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

Compared with otherwise healthy adult individuals, the clearance of amantadine hydrochloride 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 hydrochloride 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 related factors is not known.

A comparative bioavailability study was performed using normal human volunteers. The rate and extent of absorption after a single 100 mg dose of Symmetrel and phl-AMANTADINE was measured and compared. The results can be summarized as follows:

	(1) Symmetre 100 mg	(2) phl-AMANTADINE 100 mg	Ratio (2)/(1)
AUC (ng.h/mL)	5268.3	5315.2	1.01
Cmax (ng/ml)	258.1	252.2	0.98
Tmax(h)	3.7	3.75	1.01
T ½ (h)	14.06	13.27	0.94

INDICATIONS AND CLINICAL USE

INFLUENZA A, VIRUS RESPIRATORY INFECTIONS

Prophylaxis:

phl-AMANTADINE (amantadine hydrochloride) is indicated in the prevention or chemoprophylaxis of respiratory tract infections caused by Influenza A virus strains, especially in high-risk patients (including those with cardiopulmonary disease, neuromuscular disorders, the elderly, immunocompromised), close household or hospital ward contact of index cases, those in critical public service positions (e.g. police, firefighters, medical personnel).

In the prophylaxis of influenza early vaccination is the method of choice. When early vaccination is not feasible, or when the vaccine is contraindicated or not available, phl-AMANTADINE may be used for chemoprophylaxis against influenza A virus illness. It is effective against all strains of Influenza A virus which have been tested to date. Because amantadine hydrochloride does not appear to suppress antibody response, it may be given as chemoprophylaxis concurrently with inactivated Influenza A virus vaccine until protective antibodies develop. phl-AMANTADINE is not effective against other respiratory viral infections, including influenza B and parainfluenza.

Treatment:

phl-AMANTADINE is also indicated in the treatment of uncomplicated respiratory tract illness caused by influenza A virus strains. There are as yet no well-controlled studies demonstrating treatment with phl-AMANTADINE will avoid the development of influenza A virus pneumonitis or other complications in high risk patients.

There is no clinical evidence indicating that phl-AMANTADINE is effective in the prophylaxis or treatment of viral respiratory tract illnesses other than those caused by influenza A virus strains.

CONTRAINDICATIONS

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

WARNINGS

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

Patients with a history of epilepsy or other seizures should be observed closely as amantadine hydrochloride may cause increased seizure activity.

Pregnancy: Safe use of amantadine hydrochloride during pregnancy has not been established. There are no adequate and well controlled studies in pregnant women. The drug should be used during pregnancy only when the potential benefits outweigh the possible risks to the fetus (see TOXICOLOGY).

Lactation: Amantadine hydrochloride is excreted into breast milk. Amantadine hydrochloride

should not be be administered to nursing mothers.

Pediatric Use: The safety and efficacy of amantadine hydrochloride in newborn infants and infants below the age of 1 year have not been established.

PRECAUTIONS

Use in Elderly: Because amantadine hydrochloride is not metabolized and is mainly excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of amantadine hydrochloride should be reduced in patients with renal impairment and in individuals who are 65 years of age or older.

Patients with Special Diseases and Conditions: The dose of amantadine hydrochloride may need careful adjustment in patients with congestive heart failure, peripheral edema, or orthostatic hypotension.

Care should be exercised when administering amantadine hydrochloride to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when amantadine hydrochloride is administered concurrently with central nervous system stimulants.

Occupational hazards: Patients receiving amantadine hydrochloride who note CNS effects or blurring of vision should be cautioned against driving or working in situations where alertness is important.

ADVERSE REACTIONS

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

Less frequently (1-5%) reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension and headache . Infrequently (0.1-1%) occurring adverse reactions are: congestive heart failure, psychosis, urinary retention, dyspnea, fatigue, skin rash, vomiting, weakness, slurred speech and visual disturbance. Rarely (less than 0.1%) occurring adverse reactions are: instances of convulsion, leukopenia, neutropenia, eczematoid dermatitis and oculogyric episodes.

Some adverse effects were transient and disappeared often with continued administration of the drug.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms:

Overdosage has been characterized in one elderly patient who ingested 2.8 g of amantadine hydrochloride. The patient had slightly dilated pupils which contracted minimally to light, urinary retention, mild, mixed acid-base disturbances and an acute toxic psychosis manifested as disorientation, confusion, visual hallucinations, and aggressive behaviour. Convulsions did not occur, possibly because the patient had been receiving phenytoin prior to acute ingestion of amantadine hydrochloride.

Treatment:

There is no specific antidote. However, slowly administered intravenous physostigmine in 1 and 2 mg doses in an adult at 1 to 2 hours intervals and 0.5 mg doses in a child at 5 to 10 minute intervals 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 Convulsions did not occur, possibly because the patient had been receiving phenytoin prior to acute ingestion 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 hydrochloride.

Since the excretion rate of amantadine hydrochloride increases rapidly when the urine is acidic, the administration of urine acidifying drugs 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 hyperactivity and convulsions; if required, sedation and anticonvulsant therapy should be administered. The patient should be observed for the possible development of arrhythmias and hypotension; if required, appropriate antiarrhythmic and antihypotensive therapy should be given.

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 of Influenza A Virus Illness and Treatment of Uncomplicated Influenza A Virus Illness:

Normal Renal Function:

Adult: The adult daily dosage of phl-AMANTADINE (amantadine hydrochloride) 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.

9 yrs - 12 yrs of age: The total daily dose is 200 mg given as one capsule of 100 mg twice a day.

1 yrs - 9 yrs of age: The total daily dose should be calculated on the basis of 4.5 mg to 9.0 mg/kg of body weight per day (but not to exceed 150 mg per day). The daily dose should be given in two or three equal portions.

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

Creatinine Clearance ($mL/min/1.73m^2$)	phl-AMANTADINE Dosage
30-50	200 mg 1st day and 100 mg each day thereafter.
15-29	200 mg 1st day followed 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 an Influenza A outbreak and before or after contact with individuals with Influenza A virus respiratory tract illness. phl-AMANTADINE should be continued daily for at least 10 days following a known exposure.

When inactivated Influenza A virus vaccine is unavailable or contraindicated, phl-AMANTADINE should be administered for up to 90 days in case of possible repeated and unknown exposures.

Treatment of Influenza A virus illness should be started as soon as possible, preferably within 24 to 48 hours, after onset of signs and symptoms, and should be continued for 24 to 48 hours after the disappearance of signs and symptoms.

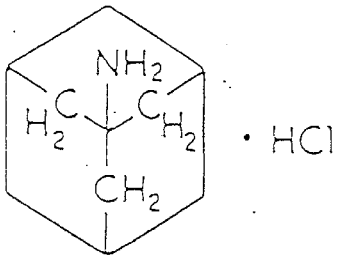
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Amantadine Hydrochloride

Chemical Name: 1-adamantanamine hydrochloride

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



Molecular Weight: 187.72

Description: Amantadine Hydrochloride is a stable white or nearly white crystalline powder which has a bitter taste and is freely soluble in water and soluble in alcohol.

Storage: Store at controlled room temperature 15˚-30˚C

AVAILABILITY OF DOSAGE FORMS

Capsules: Each red soft gelatin capsule imprinted with "0100" on one side and " Amant " on the other contains 100 mg of amantadine hydrochloride, USP. Bottles of 100 and 1000 capsules. Tartrazine free.

Syrup: Each 5 mL of clear colorless syrup contains 50 mg of amantadine hydrochloride, USP. Also contains parabens. Bottles of 250 and 500 mL. Tartrazine free.

PHARMACOLOGY

In animals, several pharmacologic effects resulted from administration of amantadine hydrochloride at relatively high doses. In mice, oral doses of 35-40 mg/Kg and above produced signs of motor activity stimulation (increased spontaneous motor activity and antagonism of tetrabenazine-induced sedation) occurred.

In dogs, a transient vasodepressor effect, cardiac arrythmias and a weak ganglionic-blocking effect were observed following intravenous doses of 13.5 mg/Kg or above. In the rat and rabbit, EEG activation has been reported with high parenteral doses.

In addition, relatively high doses of amantadine hydrochloride caused several effects in dog (potentiation of norepinephrine vasopressor response; block of phenethylamine vasopressor response; increase in myocardial contractible force) and mouse (block of norepinephrine uptake into the heart; antagonism of tetrabenazine effects) indicative of a block of uptake of norepinephrine into labile stores.

Amantadine hydrochloride is well absorbed by the oral route in all species studied. The rate of excretion of the drug is first order. The monkey and the mouse appear to metabolize it less than other animals (rat, dog and rabbit) and most nearly approximate man. There is no evidence for metabolism of the drug in man. The major route of elimination is via urine. Only the dog has been shown to convert a portion of the administered drug to its N-methylderivative which is excreted in the urine. No other metabolites have been identified.

TOXICOLOGY

Acute Toxicity:

The acute toxicity of amantadine hydrochloride by the oral, intraperitoneal, and intravenous route of administration was determined in several species of laboratory animals and the results are presented in Table 1.

TABLE 1
ACUTE TOXICITY OF
AMANTADINE HYDROCHLORIDE (56)
ID_{50} and 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]		>37
Monkey, rhesus,M	>500[a]		
Monkey, African green, F	>75		
Horse, M, F	>96		

[a] Some emesis occured.

The toxic signs produced by lethal or near-lethal doses of amantadine hydrochloride in these species were similar. Signs of central nervous system stimulation followed by tremors and brief clonic convulsions were common to the 3 rodent species by all routes of administration. Death was usually

preceded by signs of respiratory distress and convulsions. In spite of repeated convulsions, surviving animals appeared to be normal.

All deaths in small animals occurred quite promptly. In mice after intravenous doses of amantadine hydrochloride, death occurred between 7 min. and 2 hours; intraperitoneal doses caused deaths in 15 to 30 min.; oral doses between 30 min. and 2 hours. In rats, death occurred 30 min. to 2 hours after intraperitoneal doses and 30 min. to 24 hours after oral doses. In guinea pigs oral doses of amantadine hydrochloride caused most deaths between 1 and 20 hours, with a single animal dying at 44 hours. In the dog, at 93 mg/Kg and above, 3 of 4 vomited and showed all the other signs of central nervous system stimulation, including clonic convulsions, varying in intensity possibly with the amount of drug lost with emesis. One dog, which did not vomit, died at 93mg/Kg.

In rhesus monkeys, amantadine hydrochloride orally caused no deaths at any dose tested and no signs at 80 mg/Kg or less.

Chronic Toxicity:

Chronic oral toxicity experiments with amantadine hydrochloride were carried out with rats, dogs and monkeys.

Rats: Duration was 88-94 weeks with Amantadine Hydrochloride 16, 80, and 100-160 mg/Kg administered daily 5 days per week. 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.

Dogs: Duration was 2 years and amantadine hydrochloride levels were 8, 40 and 40-80 mg/Kg administered daily 5 days per week. 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 of amantadine hydrochloride/Kg, divided into two doses six hours apart, was given seven days per week for six months. No drug-related effect was seen.

Monkeys: Duration was 6 months and amantadine hydrochloride levels were 10, 40 and 100 mg/Kg administered daily 5 days per week. 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-related pathological or histo-morphological changes seen.

REPRODUCTION STUDIES

Amantadine hydrochloride was administered orally in two separate doses of 120 mg/Kg (larger dose group) and 40 mg/Kg once a day for 6 successive days from the 9th to the 14 th day of pregnancy to nullipara rats of Wistar strain at the age of 3-4 months in order to examine its effects upon the foetus during the final stage of pregnancy and on their post-natal growth. The results indicated a slight retardation of increase in the body weight of dams in the larger dose group, but amantadine hydrochloride had no effect on the nidations at the end of the final stage of pregnancy.

In the larger dose group, however, the mortality rate of the foetus and the drop in body weight of surviving litter mates showed a significant difference from those of the control group, although no deformation was observed in the group. Finally, observations on the growth of the litter mates up to the end of the 6th post-natal week in the spontaneous parturition group indicated that the parturition rate was significantly lower in the larger amantadine hydrochloride dose group than in the control group. Amantadine hydrochloride at the doses tested had no effect on suckling rate, external differentiation, survival rate, auditory senses, mobility and development of gonadal functions or skeletal structure.

Holtzman rats and New Zealand white rabbits were dosed orally with amantadine hydrochloride (0,50,100 mg/Kg) for 5 days prior to mating until day 5 of pregnancy. In rats, but not in rabbits, results of autopsies performed in day 14 of gestation showed significant decreases in the number of implantations and increases in the number of resorptions at 100 mg/Kg.

Teratology studies were performed in rats (0, 37,50 and 100 mg/Kg) by administering the drug orally on days 7-14 of gestation. Autopsy was just before expected parturition. Increases in resorption and decreases in the number of pups per litter were noted at 50 and 100 mg/Kg. Gross examination of rat pups at these dose levels revealed no malformation at 37 mg/Kg. Malformations at 50 and 100 mg/Kg included edema, malrotated hindlimbs, missing tail, stunting and brachygnatha. Examination of cleared and alizarin-stained skeletal preparations of foetuses revealed cases of absent ribs and absence of the lumbar and sacral portions of the spinal column in the 50 and 100 mg/Kg groups. Thus, in rats but not in rabbits, Amantadine seems to be embryotoxic and teratogenic. Teratogenicity in rats occurs at 50 mg/Kg/day, or about 12 times the usual human dose.

In another study doses of 10 mg/Kg in the diet had no effect on rat reproduction or lactation or number of live births. At a dose of 32 mg/Kg, fertility and lactation indices were depressed.

In another rabbit study three groups of 10 virgin female New Zealand white rabbits were dosed orally with 0,8 or 32 mg/Kg of amantadine hydrochloride from day 6 after mating through and including day 16. After 28 days the uterine contents were exposed. Amantadine hydrochloride did not alter the parameters of pregnancy or the observed characteristics of the offspring. The conception rate and incidence of resorption was similar for all groups. Litter weight and fetal loss were unaffected. Total weight and fetal loss were unaffected. Fetal weight was not significantly reduced by either dose of the drug.

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