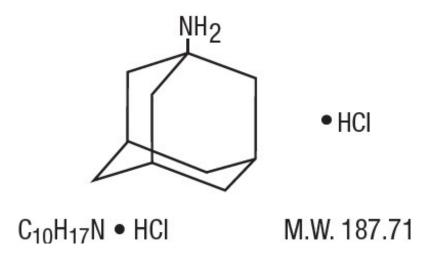
AMANTADINE- amantadine solution Xttrium Laboratories, Inc

Amantadine 16oz, 10mL Lid, Insert

Description

Amantadine hydrochloride, USP is designated generically as amantadine hydrochloride and chemically as 1-adamantanamine hydrochloride.



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

Amantadine hydrochloride has pharmacological actions as both an anti-Parkinson and an antiviral drug.

Amantadine Hydrochloride Oral Solution, USP contains 50 mg of amantadine hydrochloride per 5 mL and has the following inactive ingredients: anhydrous citric acid, artificial raspberry flavor, methylparaben, propylene glycol, propylparaben, purified water, saccharin sodium, sodium citrate dihydrate, and sorbitol solution.

Clinical Pharmacology

Pharmacodynamics

Mechanism of Action: Antiviral: The mechanism by which amantadine hydrochloride exerts its antiviral activity is not clearly understood. It appears to mainly prevent the release of infectious viral nucleic acid into the host cell by interfering with the function of the transmembrane domain of the viral M2 protein. In certain cases, amantadine hydrochloride is also known to prevent virus assembly during virus replication. It does not appear to interfere with the immunogenicity of inactivated influenza A virus vaccine. **Antiviral Activity:** Amantadine hydrochloride inhibits the replication of influenza A virus isolates from each of the subtypes, i.e., H1N1, H2N2 and H3N2. It has very little or no activity against influenza B virus isolates. A quantitative relationship between the in vitro susceptibility of influenza A virus to amantadine hydrochloride and the clinical response to therapy has not been established in man. Sensitivity test results, expressed as the

concentration of amantadine hydrochloride required to inhibit by 50% the growth of virus (ED50) in tissue culture vary greatly (from 0.1 $\hat{l}\frac{1}{4}$ g/mL to 25.0 $\hat{l}\frac{1}{4}$ g/mL) depending upon the assay protocol used, size of virus inoculum, isolates of influenza A virus strains tested, and the cell type used. Host cells in tissue culture readily tolerated amantadine hydrochloride up to a concentration of 100 $\hat{l}\frac{1}{4}$ g/mL.

Drug Resistance: Influenza A variants with reduced in vitro sensitivity to amantadine hydrochloride have been isolated from epidemic strains in areas where adamantane derivatives are being used. Influenza viruses with reduced in vitro sensitivity have been shown to be transmissible and to cause typical influenza illness. The quantitative relationship between the in vitro sensitivity of influenza A variants to amantadine hydrochloride and the clinical response to therapy has not been established. **Mechanism of Action:** Parkinson's Disease: The mechanism of action of amantadine hydrochloride in the treatment of Parkinson's disease and drug-induced extrapyramidal reactions is not known. Data from earlier animal studies suggest that amantadine hydrochloride may have direct and indirect effects on dopamine neurons. More recent studies have demonstrated that amantadine hydrochloride is a weak, noncompetitive NMDA receptor antagonist (Ki = 10Î⅓M). Although amantadine hydrochloride has not been shown to possess direct anticholinergic activity in animal studies, clinically, it exhibits anticholinergic-like side effects such as dry mouth, urinary retention, and constipation.

Pharmacokinetics

Amantadine hydrochloride is well absorbed orally. Maximum plasma concentrations are directly related to dose for doses up to 200 mg/day. Doses above 200 mg/day may result in a greater than proportional increase in maximum plasma concentrations. It is primarily excreted unchanged in the urine by glomerular filtration and tubular secretion. Eight metabolites of amantadine hydrochloride have been identified in human urine. One metabolite, an N-acetylated compound, was quantified in human urine and accounted for 5 to 15% of the administered dose. Plasma acetylamantadine accounted for up to 80% of the concurrent amantadine hydrochloride plasma concentration in 5 of 12 healthy volunteers following the ingestion of a 200 mg dose of amantadine hydrochloride. Acetylamantadine was not detected in the plasma of the remaining seven volunteers. The contribution of this metabolite to efficacy or toxicity is not known. There appears to be a relationship between plasma amantadine hydrochloride concentrations and toxicity. As concentration increases, toxicity seems to be more prevalent, however, absolute values of amantadine hydrochloride concentrations associated with adverse effects have not been fully defined.

Amantadine hydrochloride pharmacokinetics were determined in 24 normal adult male volunteers after the oral administration of a single amantadine hydrochloride 100 mg soft gel capsule. The mean $\hat{A}\pm$ SD maximum plasma concentration was 0.22 $\hat{A}\pm$ 0.03 $\hat{I}\frac{1}{4}$ g/mL (range: 0.18 to 0.32 $\hat{I}\frac{1}{4}$ g/mL). The time to peak concentration was 3.3 $\hat{A}\pm$ 1.5 hours (range: 1.5 to 8.0 hours). The apparent oral clearance was 0.28 $\hat{A}\pm$ 0.11 L/hr/kg (range: 0.14 to 0.62 L/hr/kg). The half-life was 17 $\hat{A}\pm$ 4 hours (range: 10 to 25 hours). Across other studies, amantadine hydrochloride plasma half-life has averaged 16 $\hat{A}\pm$ 6 hours (range: 9 to 31 hours) in 19 healthy volunteers.

After oral administration of a single dose of 100 mg amantadine hydrochloride in a syrup formulation to five healthy volunteers, the mean $\hat{A}\pm$ SD maximum plasmaconcentration Cmax was 0.24 \pm 0.04 µg/mL and ranged from 0.18 to 0.28 µg/mL. After 15 days of amantadine hydrochloride 100 mg b.i.d., the Cmax was 0.47 \pm 0.11 µg/mL in four of the five volunteers. Across studies, the time to Cmax (Tmax) averaged about 2 to 4 hours. Plasma amantadine hydrochloride clearance ranged from 0.2 to 0.3 L/hr/kg after the

administration of 5 mg to 25 mg intravenous doses of amantadine hydrochloride to 15 healthy volunteers.

In six healthy volunteers, the ratio of amantadine hydrochloride renal clearance to apparent oral plasma clearance was 0.79 ± 0.17 (mean \pm SD).

The volume of distribution determined after the intravenous administration of amantadine hydrochloride to 15 healthy subjects was 3 to 8 L/kg, suggesting tissue binding. Amantadine hydrochloride, after single oral 200 mg doses to 6 healthy young subjects and to 6 healthy elderly subjects has been found in nasal mucus at mean \pm SD concentrations of 0.15 \pm 0.16, 0.28 \pm 0.26, and 0.39 \pm 0.34 $\mu g/g$ at 1, 4, and 8 hours after dosing, respectively. These concentrations represented 31 \pm 33%, 59 \pm 61%, and 95 \pm 86% of the corresponding plasma amantadine hydrochloride concentrations. Amantadine hydrochloride is approximately 67% bound to plasma proteins over a concentration range of 0.1 to 2.0 $\mu g/mL$. Following the administration of amantadine hydrochloride 100 mg as a single dose, the mean \pm SD red blood cell to plasma ratio ranged from 2.7 \pm 0.5 in 6 healthy subjects to 1.4 \pm 0.2 in 8 patients with renal insufficiency.

The apparent oral plasma clearance of amantadine hydrochloride is reduced and the plasma half-life and plasma concentrations are increased in healthy elderly individuals age 60 and older. After single dose administration of 25 to 75 mg to 7 healthy, elderly male volunteers, the apparent plasma clearance of amantadine hydrochloride was 0.10 \pm 0.04 L/hr/kg (range 0.06 to 0.17 L/hr/kg) and the half-life was 29 \pm 7 hours (range 20 to 41 hours). Whether these changes are due to decline in renal function or other age related factors is not known.

In a study of young healthy subjects (n=20), mean renal clearance of amantadine hydrochloride, normalized for body mass index, was 1.5 fold higher in males compared to females (p<0.032).

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 or greater when creatinine clearance is less than 40 mL/min/1.73 m2 and averages eight days in patients on chronic maintenance hemodialysis. Amantadine hydrochloride is removed in negligible amounts by hemodialysis.

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.

Amantadine Hydrochloride Oral Solution, USP is indicated for the prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus. Amantadine hydrochloride is also indicated in the treatment of parkinsonism and drug-induced extrapyramidal reactions.

Influenza A Prophylaxis: Amantadine hydrochloride is indicated for chemoprophylaxis against signs and symptoms of influenza A virus infection. Because amantadine hydrochloride does not completely prevent the host immune response to influenza A infection, individuals who take this drug may still develop immune responses to natural disease or vaccination and may be protected when later exposed to antigenically related viruses. Following vaccination during an influenza A outbreak, amantadine hydrochloride prophylaxis should be considered for the 2- to 4-week time period required to develop an antibody response.

Influenza A Treatment: Amantadine hydrochloride is also indicated in the treatment of uncomplicated respiratory tract illness caused by influenza A virus strains especially

when administered early in the course of illness. There are no well-controlled clinical studies demonstrating that treatment with amantadine hydrochloride will avoid the development of influenza A virus pneumonitis or other complications in high risk patients.

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

The following points should be considered before initiating treatment or prophylaxis with amantadine hydrochloride:

- Amantadine hydrochloride is not a substitute for early vaccination on an annual basis as recommended by the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices.
- Influenza viruses change over time. Emergence of resistance mutations could decrease drug effectiveness. Other factors (for example, changes in viral virulence) might also diminish clinical benefit of antiviral drugs. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use amantadine hydrochloride.

Parkinson's Disease/Syndrome: Amantadine hydrochloride is indicated in the treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. It is indicated in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis. In the treatment of Parkinson's disease, amantadine hydrochloride is less effective than levodopa, (-)-3-(3,4-dihydroxyphenyl)-L-alanine, and its efficacy in comparison with the anticholinergic antiparkinson drugs has not yet been established.

Drug-Induced Extrapyramidal Reactions:

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

Contraindications

Amantadine hydrochloride is contraindicated in patients with known hypersensitivity to amantadine hydrochloride or to any of the other ingredients in Amantadine Hydrochloride Oral Solution, USP.

WARNINGS

Deaths: Deaths have been reported from overdose with amantadine hydrochloride. The lowest reported acute lethal dose was 1 gram. Acute toxicity may be attributable to the anticholinergic effects of amantadine hydrochloride. Drug overdose has resulted in cardiac, respiratory, renal or central nervous system toxicity. Cardiac dysfunction includes arrhythmia, tachycardia and hypertension (see **OVERDOSAGE**). Deaths due to drug accumulation (overdose) have been reported in patients with renal impairment, who were prescribed higher than recommended doses of amantadine

hydrochloride for their level of renal function (see **DOSAGE AND ADMINISTRATION**; Dosage of Impaired Renal Function and **OVERDOSAGE**).

Suicide Attempts: Suicide attempts, some of which have been fatal, have been reported in patients treated with amantadine hydrochloride, many of whom received short courses for influenza treatment or prophylaxis. The incidence of suicide attempts is not known and the pathophysiologic mechanism is not understood. Suicide 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 behavior, hallucinations, paranoia, other psychotic reactions, and somnolence or insomnia. Because of the possibility of serious adverse effects, caution should be observed when prescribing amantadine hydrochloride to patients being treated with drugs having CNS effects, or for whom the potential risks outweigh the benefit of treatment.

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

Patients receiving amantadine hydrochloride 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.

Other: 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 amantadine hydrochloride should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis. Because amantadine hydrochloride has anticholinergic effects and may cause mydriasis, it should not be given to patients with untreated angle closure glaucoma.

Precautions

Amantadine hydrochloride should not be discontinued abruptly in patients with Parkinson's disease since a few patients 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. Abrupt discontinuation may also precipitate delirium, agitation, delusions, hallucinations, paranoid reaction, stupor, anxiety, depression and slurred speech.

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. Therefore, patients should be observed carefully when the dosage of amantadine hydrochloride is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia; neurologic findings including muscle rigidity, involuntary movements, altered consciousness; mental status changes; other disturbances such as autonomic dysfunction, tachycardia, tachypnea, hyper- or hypotension; laboratory findings such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin.

The early diagnosis of this condition is important for the appropriate management of

these patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (e.g., pneumonia, systemic infection, etc.) is essential. This may be especially complex if the clinical presentation includes both serious medical illness 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. Dopamine agonists, such as bromocriptine, and muscle relaxants, such as dantrolene are often used in the treatment of NMS, however, their effectiveness has not been demonstrated in controlled studies.

Renal disease: Because amantadine hydrochloride 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 (see DOSAGE AND ADMINISTRATION; Dosage for Impaired Renal Function).

Liver disease: Care should be exercised when administering amantadine hydrochloride to patients with liver disease. Rare instances of reversible elevation of liver enzymes have been reported in patients receiving amantadine hydrochloride, though a specific relationship between the drug and such changes has not been established. Impulse Control/Compulsive Behaviors:

Postmarketing reports suggest that patients treated with anti-Parkinson medications can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, and other intense urges. Patients may be unable to control these urges while taking one or more of the medications that are generally used for the treatment of Parkinson's disease and that increase central dopaminergic tone, including Amantadine hydrochloride. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with Amantadine hydrochloride. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking amantadine hydrochloride.

Melanoma:

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear. For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using amantadine hydrochloride for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Other: 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 a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents.

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. Amantadine hydrochloride has not been shown to prevent such complications.

Information for Patients: Patients should be advised of the following information: Blurry vision and/or impaired mental acuity may occur.

Gradually increase physical activity as the symptoms of Parkinson's disease improve. Avoid excessive alcohol usage, since it may increase the potential for CNS effects such as dizziness, confusion, lightheadedness and orthostatic hypotension.

Avoid getting up suddenly from a sitting or lying position. If dizziness or lightheadedness occurs, notify physician.

Notify physician if mood/mental changes, swelling of extremities, difficulty urinating and/or shortness of breath occur.

Do not take more medication than prescribed because of the risk of overdose. If there is no improvement in a few days, or if medication appears less effective after a few weeks, discuss with a physician.

Consult physician before discontinuing medication. Seek medical attention immediately if it is suspected that an overdose of medication has been taken.

Drug Interactions: Careful observation is required when amantadine hydrochloride is administered concurrently with central nervous system stimulants.

Agents with anticholinergic properties may potentiate the anticholinergic-like side effects of amantadine hydrochloride.

Coadministration of thioridazine has been reported to worsen the tremor in elderly patients with Parkinson's disease, however, it is not known if other phenothiazines produce a similar response.

Coadministration of triamterene/hydrochlorothiazide resulted in a higher plasma amantadine hydrochloride concentration in a 61-year-old man receiving amantadine hydrochloride 100 mg TID for Parkinson's disease.1 It is not known which of the components of triamterene/hydrochlorothiazide contributed to the observation or if related drugs produce a similar response.

Coadministration of quinine or quinidine with amantadine hydrochloride was shown to reduce the renal clearance of amantadine hydrochloride by about 30%.

The concurrent use of amantadine hydrochloride with live attenuated influenza vaccine (LAIV) intranasal has not been evaluated. However, because of the potential for interference between these products, LAIV should not be administered within 2 weeks before or 48 hours after administration of amantadine hydrochloride, unless medically indicated. The concern about possible interference arises from the potential for antiviral drugs to inhibit replication of live vaccine virus. Trivalent inactivated influenza vaccine can be administered at any time relative to use of amantadine hydrochloride.

Carcinogenesis, Mutagenesis: Long-term in vivo animal studies designed to evaluate the carcinogenic potential of amantadine hydrochloride have not been performed. In several in vitro assays for gene mutation, amantadine hydrochloride did not increase the number of spontaneously observed mutations in four strains of Salmonella typhimurium (Ames Test) or in a mammalian cell line (Chinese Hamster Ovary cells) when incubations were performed either with or without a liver metabolic activation extract. Further, there was no evidence of chromosome damage observed in an in vitro test using freshly derived and stimulated human peripheral blood lymphocytes (with and without metabolic activation) or in an

in vivo mouse bone marrow micronucleus test (140 to 550 mg/kg; estimated human equivalent doses of 11.7 to 45.8 mg/kg based on body surface area conversion). **Impairment of Fertility:** The effect of amantadine hydrochloride on fertility has not been adequately tested, that is, in a study conducted under Good Laboratory Practice

(GLP) and according to current recommended methodology. In a three litter, non-GLP,

reproduction study in rats, amantadine hydrochloride at a dose of 32 mg/kg/day (equal to the maximum recommended human dose on a mg/m2 basis) administered to both males and females slightly impaired fertility. There were no effects on fertility at a dose level of 10 mg/kg/day (or 0.3 times the maximum recommended human dose on a mg/m2 basis); intermediate doses were not tested.

Failed fertility has been reported during human in vitro fertilization (IVF) when the sperm donor ingested amantadine hydrochloride 2 weeks prior to, and during the IVF cycle.

Pregnancy:

Teratogenic Effects: The effect of amantadine hydrochloride on embryofetal and peripostnatal development has not been adequately tested, that is, in studies conducted under Good Laboratory Practice (GLP) and according to current recommended methodology. However, in two non-GLP studies in rats in which females were dosed from 5 days prior to mating to Day 6 of gestation or on Days 7 to 14 of gestation, amantadine hydrochloride produced increases in embryonic death at an oral dose of 100 mg/kg (or 3 times the maximum recommended human dose on a mg/m2 basis). In the non-GLP rat study in which females were dosed on Days 7 to 14 of gestation, there was a marked increase in severe visceral and skeletal malformations at oral doses of 50 and 100 mg/kg (or 1.5 and 3 times, respectively, the maximum recommended human dose on a mg/m2 basis). The no-effect dose for teratogenicity was 37 mg/kg (equal to the maximum recommended human dose on a mg/m2 basis). The safety margins reported may not accurately reflect the risk considering the questionable quality of the study on which they are based. There are no adequate and well-controlled studies in pregnant women. Human data regarding teratogenicity after maternal use of amantadine hydrochloride is scarce. Tetralogy of Fallot and tibial hemimelia (normal karyotype) occurred in an infant exposed to amantadine hydrochloride during the first trimester of pregnancy (100 mg P.O. for 7 days during the 6th and 7th week of gestation). Cardiovascular maldevelopment (single ventricle with pulmonary atresia) was associated with maternal exposure to amantadine hydrochloride (100 mg/d) administered during the first 2 weeks of pregnancy. Amantadine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

Nursing Mothers: Amantadine hydrochloride is excreted in human milk. Use is not recommended in 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.

Usage in the Elderly: Because amantadine hydrochloride is primarily 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. The dose of amantadine hydrochloride may need reduction in patients with congestive heart failure, peripheral edema, or orthostatic hypotension (see DOSAGE AND ADMINISTRATION).

Adverse Reaction

The adverse reactions reported most frequently at the recommended dose of amantadine hydrochloride (5 to 10%) are: nausea, dizziness (lightheadedness), and insomnia.

Less frequently (1 to 5%) reported adverse reactions 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 (0.1 to 1%) occurring adverse reactions are: congestive heart failure, psychosis, urinary retention, dyspnea, skin rash, vomiting, weakness, slurred speech, euphoria, thinking abnormality, amnesia, hyperkinesia, hypertension, decreased libido, and visual disturbance, including punctate subepithelial or other corneal opacity, corneal edema, decreased visual acuity, sensitivity to light, and optic nerve palsy.

Rare (less than 0.1%) occurring adverse reactions are:

instances of convulsion, leukopenia, neutropenia, eczematoid dermatitis, oculogyric episodes, suicidal attempt, suicide, and suicidal ideation (see **WARNINGS**).

Other adverse reactions reported during postmarketing experience with amantadine hydrochloride usage include:

Nervous System/Psychiatric: coma, stupor, delirium, hypokinesia, hypertonia, delusions, aggressive behavior, paranoid reaction, manic reaction, involuntary muscle contractions, gait abnormalities, paresthesia, EEG changes, and tremor. Abrupt discontinuation may also precipitate delirium, agitation, delusions, hallucinations, paranoid reaction, stupor, anxiety, depression and slurred speech;

Cardiovascular: cardiac arrest, arrhythmias including malignant arrhythmias, hypotension, and tachycardia;

Respiratory: acute respiratory failure, pulmonary edema, and tachypnea;

Gastrointestinal: dysphagia;

Hematologic: leukocytosis and agranulocytosis;

Special Senses: keratitis and mydriasis;

Skin and Appendages: pruritus and diaphoresis;

Miscellaneous: neuroleptic malignant syndrome (see WARNINGS), allergic reactions including anaphylactic reactions, edema, and fever;

Laboratory Test: elevated: CPK, BUN, serum creatinine, alkaline phosphatase, LDH, bilirubin, GGT, SGOT, and SGPT.

Overdosage

Deaths have been reported from overdose with amantadine hydrochloride. The lowest reported acute lethal dose was 1 gram. Because some patients have attempted suicide by overdosing with amantadine hydrochloride, prescriptions should be written for the smallest quantity consistent with good patient management.

Acute toxicity may be attributable to the anticholinergic effects of amantadine hydrochloride. Drug overdose has resulted in cardiac, respiratory, renal or central nervous system toxicity. Cardiac dysfunction includes arrhythmia, tachycardia and hypertension. Pulmonary edema and respiratory distress (including adult respiratory distress syndrome -- ARDS) have been reported; renal dysfunction including increased BUN, decreased creatinine clearance and renal insufficiency can occur.

Central nervous system effects that have been reported include insomnia, anxiety, agitation, aggressive behavior, hypertonia, hyperkinesia, ataxia, gait abnormality, tremor, confusion, disorientation, depersonalization, fear, delirium, hallucinations, psychotic reactions, lethargy, somnolence and coma. Seizures may be exacerbated in patients with prior history of seizure disorders. Hyperthermia has also been observed in cases where a drug overdose has occurred.

There is no specific antidote for an overdose of amantadine hydrochloride. However, slowly administered intravenous physostigmine in 1 and 2 mg doses in an adult2 at 1- to 2-hour intervals and 0.5 mg doses in a child3 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. 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. Electrocardiographic monitoring may be required after ingestion, since malignant tachyarrhythmias can appear after overdose. Care should be exercised when administering adrenergic agents, such as isoproterenol, to patients with an amantadine hydrochloride overdose, since the dopaminergic activity of amantadine hydrochloride has been reported to induce malignant arrhythmias. The blood electrolytes, urine pH and urinary output should be monitored. If there is no record of recent voiding, catheterization should be done.

The dose of amantadine hydrochloride may need reduction in patients with congestive heart failure, peripheral edema, orthostatic hypotension, or impaired renal function (see Dosage for Impaired Renal Function).

Dosage for Prophylaxis and Treatment of Uncomplicated Influenza A Virus Illness:

Adult: The adult daily dosage of amantadine hydrochloride is 200 mg (four teaspoonfuls of oral solution) as a single daily dose. The daily dosage may be split into two teaspoonfuls of oral solution twice a day. If central nervous system effects develop in once-a-day dosage, a split dosage schedule may reduce such complaints. In persons 65 years of age or older, the daily dosage of amantadine hydrochloride is 100 mg.

A 100 mg daily dose has also been shown in experimental challenge studies to be effective as prophylaxis in healthy adults who are not at high risk for influenza-related complications. However, it has not been demonstrated that a 100 mg daily dose is as effective as a 200 mg daily dose for prophylaxis, nor has the 100 mg daily dose been studied in the treatment of acute influenza illness. In recent clinical trials, the incidence of central nervous system (CNS) side effects associated with the 100 mg daily dose was at or near the level of placebo. The 100 mg dose is recommended for persons who have demonstrated intolerance to 200 mg of amantadine hydrochloride daily because of CNS or other toxicities.

Pediatric Patients: 1 yr. to 9 yrs. of age: The total daily dose should be calculated on the basis of 2 to 4 mg/lb/day (4.4 to 8.8 mg/kg/day), but not to exceed 150 mg per day.

9 yrs. to 12 yrs. of age: The total daily dose is 200 mg given as two teaspoonfuls of oral solution twice a day. The 100 mg daily dose has not been studied in this pediatric population. Therefore, there are no data which demonstrate that this dose is as effective as or is safer than the 200 mg daily dose in this patient population. 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. Amantadine hydrochloride should be continued daily for at least 10 days following a known exposure. If amantadine hydrochloride is used chemoprophylactically in

conjunction with inactivated influenza A virus vaccine until protective antibody responses develop, then it should be administered for 2 to 4 weeks after the vaccine has been given. When inactivated influenza A virus vaccine is unavailable or contraindicated, amantadine hydrochloride should be administered for the duration of known influenza A in the community because of repeated and unknown exposure.

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.

Dosage for Parkinsonism:

Adult: The usual dose of 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 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, if necessary.

Occasionally, patients whose responses are not optimal with amantadine hydrochloride at 200 mg daily may benefit from an increase up to 400 mg daily individed doses. However, such patients should be supervised closely by their physicians. Patients initially deriving benefit from amantadine hydrochloride 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 amantadine hydrochloride 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 amantadine hydrochloride. When amantadine hydrochloride or anticholinergic antiparkinson drugs are each used with marginal benefit, concomitant use may produce additional benefit.

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

When amantadine hydrochloride 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 amantadine hydrochloride.

Dosage for Drug-Induced Extrapyramidal Reactions:

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

Dosage for Impaired Renal Function:

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

CREATININE AMANTADINE CLEARANCE HYDROCHLORIDE

(mL/min/1.73m²) DOSAGE

30 to 50 200 mg 1st day and

100 mg each day thereafter

15 to 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.

How Supplied

Amantadine Hydrochloride Oral Solution, USP 50 mg/5 mL is a colorless to pale yellow, raspberry-flavored oral solution available in:

10 mL unit dose cups in trays of 10 (NDC 0116-4010-10)

1 Pint (473 mL) bottles (NDC 0116-4010-16)

Store at 20° to 25°C (68° to 77°F), excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature].

KEEP TIGHTLY CLOSED

Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).

Rx Only

References

1W.W. Wilson and A.H. Rajput, Amantadine-Dyazide Interaction, Can. Med. Assoc. J. 129:974-975, 1983.

2D.F. Casey, N. Engl. J. Med. 298:516, 1978.

3C.D. Berkowitz, J. Pediatr. 95:144, 1979.

Manufactured by:

Xttrium Laboratories, Inc.

1200 E. Business Center Dr.

Mount Prospect, IL 60056

4010AMANINSTA

Amantadine 16oz Label

Lift Here

Each 5 mL (1 teaspoonful) contains: Amantadine Hydrochloride, USP 50 mg

USUAL DOSAGE: See accompanying package insert for complete prescribing information.

WARNINGS: KEEP THIS AND ALL DRUGS OUT OF THE REACH

In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

Store at 20° to 25°C (68° to 77°F), excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]. KEEP TIGHTLY CLOSED

Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).

Manufactured by: Xttrium Laboratories, Inc. 1200 E. Business Center Dr. Mount Prospect, IL 60056

4010160ZLBLA REV.08-24





NDC 0116-4010-16

AMANTADINE HYDROCHLORIDE **ORAL SOLUTION, USP** 50 mg/5 mL

DO NOT USE IF TAMPER-EVIDENT SEAL IS BROKEN OR MISSING.

Rx Only



NET: 1 Pint (473 mL)

DE SCRIPTION

Amantadine hydrochloride, USP is designated generically as a chemically as 1-adamantanamine hydrochloride.

ICI MW.187.71 ite or nearly white crystalline power condorm.

Nydrodkride Oral Solution, USP contains 50 mg of amantadine hydrochloride thas the following in active ingredients: anhydrous citric acid, artificial respictory liganitien; propylere glyto, propyleanitien, purified water, saccharin zodium, te dhydrate, and sorbitol solution.

hlonde inhibits the replication of influenza A virus H1N1, H2N2 and H3N2. It has very little or no activit artitative relationship between the *in vitro*

abiento el nebito Privincion's Diseases. The mechanism of action of annutrafine blaction in the teament of displancion's design and thrus photose for any armind sor is not known. Data from order arisinal studies suggest that annutrafine blaction may have alreat any indirect effects on dopmaine memors. More prosed studies benerotirated that annutrafies hydrochloride is a week, non-competitive MIDA. For any parties (K.)—EMAR MATONIS manufacture by troublock has not been at down to an effect and blacting activity in annual studies, already, it entails a market and blacting activity in annual studies, already, it entails are an effect and blacting activity in annual studies, and many restrictive, and complication. n dopamine neurons. More recent studies a week, non-competitive MMDA as week, non-competitive bmDA the hydrochloride has not been shown to es, clinically, it exhibits urinary retention, and constipation.

Anamatical by profektide pharmaciónnics were determinach? A narmal add male volumber, dier the role alimente for of a singe amantine phasholde (10 mg set couple. The men — 50 maximum obsens concentration was 102 ± 0.00 yprin. (I opay, 10 18 to 102 yprin.). The singe to profession was 102 ± 0.00 yprin. (I opay, 10 18 to 102 yprin.). The profession of the concentration was 102 ± 0.00 yprin. (I opay, 10 to 100 yprin.). The singe to profession was 10 ± 0.00 yprin. (I opay, 10 ± 0.00 yprin.). The singe to the concentration of t mete appears to be a reliaborship between plasma amartadine hydrochloride concentrations and touch y, de concentration increases, touchy seems to be more prevalent, however, about be values of amartadine hydrochloride concentrations associated with adverse effects teve not been fully defined.

hydrocheric planna half it is nie enroged 16 ± 6 livers (impe 2 to 31 livera) in 19 healty viurteens.

Alter cell administration of a single done of 100 mg mentidien bydrocherich in a prup formulation by the studies.

Alter cell administration of a single done of 100 mg mentidien bydrocherich in a prup formulation in the studies.

Alter cell administration of 10 mg mentidien bydrocherich in a prup formulation by the studies.

Remainment of 10 mg but, the Care, we make 10 mg but 10

vder, freely soluble

e hydrochloride has pharmacological actions as both an anti-Parkinson and an

Inrug-Induc ed Echrayyam ital Recitions:

Amusilatine hydrochorie is included in the treatment of drug-included extragramatial funcations. Although anticipolineppic-type side effects have been noted with amusilatine phydrochories when used in jacteris with drug-included extragramatial recorders, there is a flyther including a second of each in his had been very with the anticipolinepic in case side effects than that observed with the anticipolinepic in case side effects than that observed with the anticipolinepic in case.

CONTRAIND CATIONS

Amanbaline by drochloride is contrain disabled in patients with known by personsitivity to an amanbaline by drochloride or to any of the other ingredients in Amanbaline Hydrochloride Oral Solidan, USP.

De affer. Deaths lavel hear reported from overfices with annandarie hydrochloride. The lowest reported acute lettled does was 1 gram. Acute tousoity may be artimutable to the enablishinerary effects of annantations by drochloride. Drug overdoes has resulted in cardiac, respiratory, rend or central nervous speam toxicity. Cardiac dysfunction includes arrhythmia fauthy-cardia and hypertension (see OFENDOSAGE).

Suicide Attempts: Suicide attempts, some of which have been fatal, have been reported in patients treated with amenitative hydrochloride, many of whom received abort our sess for influence to receive the control of the patients treated with amenitative hydrochloride, many of whom received abort our sess for influence to the pathophy subagic merchanism is not undestood. Suicide attempts and suicidial deathon have been reported in patients with an advantural problems in patients with a listory of psychiatric disease. Anautacidine hydrochloride can excerdate mental problems in patients with a listory of psychiatric disease. Anautacidine describes or substations abuses Patients who attempts such at homeometic advantage against a described in patients which include disorientation, confusion, depression, personally changes, against, against which include disorientation, confusion, depression, personally changes, against, against which include disorientation, confusion, depression, personally changes, against, against which include disorientation, confusion, depression, personally changes, against against a patient which include a supplication, against a productive depression, personally changes, against against a patient by a patient being treated with our put having CNS effects, patients with a listory of epigepy or other "secures" should be observed cheep for possible increased secure advity.

Discription of the patient of the patient of the patient and patients with a listory of epigepy or other "secures" should be observed a cheep for possible increased secure advity.

Distincts receiving amentatine hydrochloride who note central nervous system effects or burning of vision should be cautioned against driving or working in situations where eleftness and adequate motor coordination are important. Offer: Patients with a history of congestive heart failure or peripheral echema should be followed closely as there are patients who developed congestive heart failure while receiving amantations hydrochloride.

Paleints with Parkinson's disease improving on amantatine hydrochloride should resume normal adviries gnadually and eautiously, consistent with other medical consider afuns, such as the presence of osteoporouss or philebolthrombosis.

Amenation by drochloride should not be discontinued abrupth in potients with Parkinson's disease since a few preferrations there experienced a participational or risk; at, a sudden marked chinical desiruction, when this medication was subberly stopped. The does of anticipationerspic drugs or of amenatatine hydrochloride should be reduced if attorpie-like effects appear, when these drugs are used concurrently. Abrupt discontinuation may also precipitate of cifium, agilation, ebusions, hallucinations, paramoid reaction, stupor, anxiety, depression and sturred speech.

INDICATIONS AND USAGE Amantadine Hydrochloride

cride Oral Solution, USP is indicated for the prophylaxis and treatment of of infection caused by various strains of influenza A virus. Amantadine indicated in the treatment of parkinsonism and drug-induced

Influenza A Pophylaxis Annahaline Inydochloride is indicated for demographicasis against signs and symboths of influenza A rina; infection. Because anaihaline lydochloride does not completely present the host immune response to influenza A rina; infection, individuals not bate fish during pany still develop immune responses to natural desease or vaccination and may be protected when later exposed to stiliparically related vinces. Following vaccination developed in influenza A activates, a narradiate hydrochloride prophylaxis should be considered for the 2- to 4-week time period required to develop an analysis should be considered for the 2- to 4-week time period required to develop an analysis should be considered for the 2- to 4-week time period required to develop an analysis of the second control of

Influenza A Treatment: Amantadine hydrochloride is also indicated in the treatment of uncomplicated respiratory tract illness caused by influenza A virus strains especially when administered early in the ourse of iliness. There are no well-controlled clinical studies bemorstrating that treatment with anantadien bytochoricide will avoid the development of influenza A virus pneumonitis or other complications in high risk patients.

There is no dinical evidence indicating that amantadine by drochloride is effective in the prophylaxis or treatment of viral respiratory tractill nesses other than those caused by

The following points should be considered before initiating treatment or prophylaxis with amantadine hydrochloride:

Amantadine hydrochloride is not a substitute for early vaccination on an annual basis as recommended by the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices.

Influenza viuses obango over time. Emergence of resistance mutations could decrease drug effectiveness. Other factors (for example, changes invital virulence) might also diminish chinical benefit of antivital drugs, Prescribers stood consister available. information on influenza drug susceptibility patterns and treatment effects when deciding whether to use amantadine hydrochloride.

Parkinson's Disease/Syndrom et Amantadine hydrochloride is indicated in the treatment of idiopatile Parkinson's disease (Panalysis Agharis), postenosphalife parkinsonism, and symdromatic parkinsonism which may follow injury for the nervous system by anbon morooxide indoxisation, it is indicated in those elderly patients believed to develop parkinsonism in association with creft all articipatements. In the treatment of Parkinson's desease amentadine hydrochloride is less effective than terochopa. (1-3-5) 4, 4-ditydroxyhorsyll-1-adminis and its efficacy in comparison with the anticholinergic antiparkinson drugs has not yet been established.

Deaths due to drug accumulation (overcboe) have been reported in patients with renal impairment, who were prescribed injuier than recommended doess of annantaofine importance, who were prescribed to the control (see DOSAGE AND ADMINISTRATION; Dosage of impairmed Renal Function and OVERDOSAGE).

Because amantadine hydrochloride should not be given to patients with has anticholinergic effects and may cause mydnasis, it nuntreated angle closure glaucoma.

Neuroleptic Malignant Syndrome (NMS): Sporadic cases of possible Neuroleptic Malignant Syndrome (NMS) have been reported in association with dose reduction or withdrawal of amandatine lydrochoride therapy. Therefore, patients should be observed carefully when the dosage of amandatine hydrochloride is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

neurologic findings including muscle rigidity, involuntary movements, aftered consciousness; mental status changes; other disturbances such as authoriomic dysfunction, tachycardia, tachypinea, hyper- or hypotension; laboratory findings such as creatine phosphokinase NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia; elevation, leuko cytosis, myoglobinuna, and increased serum myoglobin

patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (e.g., petients, systemic infection, etc.) is essential. This may be especially complex if the preumonia, systemic infection, etc.) is essential. This may be especially complex if the preumonia greentation includes both serious medical illness and untreated or inadequately clinical presentation includes both serious medical illness and untreated or inadequately clinical presentation includes both serious medical illness. primary central nervous system (CNS) pathology. treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and he early diagnosis of this condition is important for the appropriate management of these

treatments are available. Dopamine agonists, such as bromocriptine, and muscle relaxants, such as dantrolene are often used in the treatment of NMS, however, their effectiveness has not been demonstrated in controlled studies monitoring, and 2) treatment of any concomitant serious medical problems for which specific The management of NMS should include: 1) intensive symptomatic treatment and medical

Renal disease: Because amantadine hydrochloride is mainly excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of for Impaired Renal Function) amantadine hydrochloride should be reduced in patients with renal impairment and in individuals who are 65 years of age or older (see DOSAGE AND ADMINISTRATION; Dosage

patients with liver disease. Rare instances of reversible elevation of liver erzymes have been reported in patients receiving amantadine hydrochloride, though a specific relationship between the Liver disease: Care should be exercised when administering amantadine hydrochloride to drug and such changes has not been established

mpulse Control/Compulsive Behaviors:

hydrochloride. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, Postmarketing reports suggest that patients treated with anti-Parkinson medications can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, and other intense urges. Patients may be unable to control these urges while taking one or more of the medications that are generally used for the treatment of Parkinson's disease and that increase central dopaminergic tone, including Amantadine pauerius or ureir caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with Amantadine hydrochloride. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking amantadine hydrochloride

(2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear. pidemiological studies have shown that patients with Parkinson's disease have a higher risk-

frequently and on a regular basis when using amantadine hydrochloride for any indication. For the reasons stated above, patients and providers are advised to monitor for melanomas periodic skin examinations should be performed by appropriately qualified individuals

Other: 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 a history of recurrent eczemato id rast, or to patients with psychosis or severe psychoneurosis not

Serious bacterial infections may begin with influenza-like symptoms or may coexist with occur as complications during the course of influenza. A mantadine hydrochloride has not been shown to prevent such complications.

Information for Patients: Patients should be advised of the following information:

Blurry vision and/or impaired mental acuity may occur.

Avoid excessive alcohol usage, since it may increase the potential for CNS effects such as dizziness, confusion, lightheadedness and orthostatic hypotension. Gradually increase physical activity as the symptoms of Parkinson's disease improve.

Avoid getting up suddenly from a sitting or lying position. If dizziness or lightheadedness

shortness of breath occur Notify physician if mood/mental changes, swelling of extremities, difficulty urinating and/or

Do not take more medication than prescribed because of the risk of overdose. If there is no improvement in a few days, or if medication appears less effective after a few weeks, discuss with a physician.

Consult physician before discontinuing medication. suspected that an overdose of medication has been of medication has been . Seek medical attention immediately if it is n taken.

> administered concurrently with central nervous system stimulants Drug Interactions: Careful observation is required when amantadine hydrochloride is

amantadine hydrochloride Agents with anticholinergic properties may potentiate the anticholinergic-like side effects of

with Parkinson's disease, however, it is not known if other phenothiazines produce a similar Coadministration of thioridazine has been reported to worsen the tremor in elderly patients

Coadministration of triamterene/hydrochlorothiazide resulted in a higher plasma amantadine riamterene/hydrochlorothiazide contributed to the observation or if related drugs produce a nydrochloride concentration in a 61-year-old man receiving amantadine hydrochloride 100 mg TID for Parkinson's disease. 1 It is not known which of the components of

Coadministration of quinine or quinidine with amantadine hydrochloride was shown to reduce the renal clearance of amantadine hydrochloride by about 30%. sımılar response.

after administration of amantadine hydrochloride, unless med cally indicated. The concern about possible interference arises from the potential for arthiviral drugs to inhibit replication of live vaccine virus. Trivatent inactivated influenza vaccine can be administered at any time. relative to use of amantadine hydrochloride. between these products, LAIV should not be administered within 2 weeks before or 48 hours The concurrent use of amantadine hydrochloride with live attenuated influenza vaccine (LAV) intranasal has not been evaluated. However, because of the potential for interference

Carcinogenesis, Mutagenesis: Long-term in vivo animal studies designed to evaluate the carcinogenic potential of amantadine hydrochloride have not been performed. In several in vitro assays for gene mutation, amantadine hydrochloride did not increase the number of chromosome damage observed in an *in vitro* test using freshly derived and stimulated human peripheral blood lymphocytes (with and without metabolic activation) or in an *in vivo* mouse bone marrow micronucleus test (140 to 550 mg/kg; estimated human equivalent doses of spontaneously observed mutations in four strains of Salmonella typhimurium (Ames Test) or in a mammalian cell line (Chinese Hamster Ovary cells) when incubations were performed either with or without a liver metabolic activation extract. Further, there was no evidence of 11.7 to 45.8 mg/kg based on body surface area conversion).

Impairment of Fertility. The effect of amantadine hydrochloride on fertility has not been adequately tested, that is, in a study conducted under Good Laboratory Practice (GLP) and according to current recommended methodology. In a three litter, non-GLP, reproduction study in rats, amantadine hydrochloride at a dose of 32 mg/kg/day (equal to the maximum recommended human dose on a mg/m²-basis) administered to both males and females slightly impaired fertility. There were no effects on fertility at a dose level of 10 mg/kg/day (equal) were not tested the maximum recommended human dose on a mg/m² basis); intermediate doses ĝ

Failed fertility has been reported during human in vitro fertilization (NF) when the sperm donor ingested amantadine hydrochloride 2 weeks prior to, and during the NF cycle.

peri-postnatal development has not been adequately tested, that is, in studies conducted under Good Laboratory Practice (GLP) and according to current recommended methodology However, in two non-GLP studies in rats in which females were dosed from 5 days prior to Cardiovascular maldevelopment (single ventride with pulmonary atresia) was associated with maternal exposure to amantadine hydrochloride (100 mg/d) administered during the first 2 a mg/m² basis). The safety margins reported may not accurately reflect the risk considering the questionable quality of the study on which they are based. There are no adequate and females were dosed on Days 7 to 14 of gestation, there was a marked increase in severe visceral and skeletal malformations at oral doses of 50 and 100 mg/kg (or 1.5 and 3 times, respectively, the maximum recommended human dose on a mg/m² basis). The no-effect mating to Day 6 of gestation or on Days 7 to 14 of gestation, amantadine hydrochloride produced increases in embryonic death at an oral dose of 100 mg/kg (or 3 times the well-controlled studies in pregnant women. Human data regarding teratogenicity after maternal use of amantadine hydrochloride is scarce. Tetralogy of Fallot and tibial hemimelia dose for teratogenicity was 37 mg/kg (equal to the maximum recommended human dose on potential benefit justifies the potential risk to the embryo or fetus weeks of pregnancy. Amantadine hydrochloride should be used during pregnancy only if the normal karyotype) occurred in an infant exposed to amantadine hydrochloride during the first maximum recommended human dose on a mg/m² basis). In the non-GLP rat study in which rimester of pregnancy (100 mg P.O. for 7 days during the 6th and 7th week of gestation) *Teratogenic Effects:* The effect of amantadine hydrochloride on embryofetal and

recommended in nursing mothers. lursing Mothers: Amantadine hydrochloride is excreted in human milk. Use is not

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

individuals who are 65 years of age or older. The dose of amantadine hydrochloride may need reduction in patients with congestive heart failure, peripheral edema, or orthostatic 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 **Usage in the Elderly:** Because amantadine hydrochloride is primanly excreted in the urine, it patients with congestive heart failure, peripheral edema, or orthostatic (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The adverse reactions reported most frequently at the recommended dose of amantadine hydrochloride (5 to 10%) are: nausea, dizziness (lightheadedness), and insomnia.

ess frequently (1 to 5%) reported adverse reactions are:

abnormality, amnesia, hyperkinesia, hypertension, decreased libido, and visual disturbance, including punctate subepithelial or other corneal opacity, corneal edema, decreased visual unnary retention, dyspnea, skin rash, vomiting, weakness, slurred speech somnolence, nervousness, dream abnormality, agitation, dry nose, diarrhea and fatigue. constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension, nfrequently (0.1 to 1%) occurring adverse reactions are: congestive heart failure, psychosis, depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth euphoria, thinking , headache,

acuity, sensitivity to light, and optic nerve palsy. Rare (less than 0.1%) occurring adverse reactions are:

instances of convulsion, leukopenia, neutropenia, eczematoid dermatitis, oculogyric episodes suicidal attempt, suicide, and suicidal ideation (see WARNINGS).

hydrochloride usage include: Other adverse reactions reported during postmarketing experience with amantadine

Nervous System/Psychiatric: coma, stupor, delirium, hypokinesia, hypertonia, delusions, aggressive behavior, paranoid reaction, manic reaction, involuntary muscle contractions, gait abnormalities, paresthesia, EEG changes, and tremor. Abrupt discontinuation may also precipitate delirium, agitation, delusions, hallucinations, paranoid reaction, stupor, anxiety

Cardiovascular: cardiac arrest, arrhythmias including malignant arrhythmias, hypotension,

depression and slurred speech

Respiratory: acute respiratory failure, pulmonary edema, and tachypnea;

Gastrointestinal: dysphagia;

Special Senses: keratitis and mydriasis; Hematologic: leukocytosis and agranulocytosis;

Skin and Appendages: pruritus and diaphoresis;

Miscellaneous: neuroleptic malignant syndrome (see WARNINGS), allergic reactions including anaphylactic reactions, edema, and fever;

GGT, SGOT, and SGPT. aboratory Test: elevated: CPK, BUN, serum creatinine, alkaline phosphatase, LDH, bilirubin.

OVERDOSAGE

Deaths have been reported from overdose with amantadine hydrochloride. The lowest reported acute lethal dose was 1 gram. Because some patients have attempted suicide by overdosing with amantadine hydrochloride, prescriptions should be written for the smallest quantity consistent with good patient management

Acute toxicity may be attributable to the anticholinergic effects of amantadine hydrochloride Drug overdose has resulted in cardiac, respiratory, renal or central nervous system toxicity. Cardiac dysfunction includes arrhythmia, tachycardia and hypertension. Pulmonary edema and respiratory distress (including adult respiratory distress syndrome — ARDS) have been insufficiency can occur. renal dysfunction including increased BUN, decreased creatinine clearance and

Central nervous system effects that have been reported include insomnia, anxiety, agitation, aggressive behavior, hypertonia, hypertoniesia, ataxia, gait abnomatily, termor, confusion, disorientation, depersonalization, fear, delinium, hallucinations, psychotic reactions, lethargy, somnolence and coma. Sezures may be exacerbated in patients with prior history of sezure disorders. Hyperthermia has also been observed in cases where a drug overdose has occurred.

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. The pH of the urine has been reported to influence the excretion rate of amantaddine hydrochloride. Since the excretion rate of amantadnine hydrochloride increases rapidly when the urine is acide, the administration of 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 There is no specific artidote for an overdose of amantadine hydrochloride. However, slowly administered intravenous physostigmine in 1 and 2 mg doses in an adult² at 1- to 2-hour intervals and 0.5 mg doses in a child³ at 5- to 10-minute intervals up to a maximum 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 2 mg/hour have been reported to be effective in the control of central nervous system toxicity since malignant tachyarrhythmias can appear after overdose herapy should be given. Electrocardiographic monitoring may be required after

Care should be exercised when administering adrenergic agents, such as isoproterenol an amantadine hydrochloride overdose, since the dopaminergic activity 0 ਰ

The blood electrolytes, urine pH and urinary output should be monitored. If there is no record amantadine hydrochlonde has been reported to induce malignant arrhythmias.

DOSAGE AND ADMINISTRATION
The dose of amantadine hydrocelog

Impaired Renal Function).

Dosage for Prophylaxis and Treatment of Uncomplicated Influenza A Virus Illness hydrochloride may need reduction in patients with congestive heart t, orthostatic hypotension, or impaired renal function (see **Dosage for**

sage of amantadine hydrochloride is 200 mg (four teaspoonfuls of daily dose. The daily dosage may be split into two teaspoonfuls of if central nenous system effects develop in once-a-day dosage, a ay reduce such complaints.

In persons 65 years of age or older, the daily decage of amantadine hydrochloride in 100 mg. A 100 mg daily does have also been down in asperimental challenge studies to be effective as probligates in the simply yablos where are led it full intellect inflience desided complications, as probligates in the simply yablos where are led it full intellect ended complications, as probligates in the simply yablos where are led it full intellect ended complications, as the problem complication in the treatment of ladily reds. It is purphyelia, conclusion that 0,00 mg daily does was at or near the level of placebi. The 100 mg daily does have at or ones the level of placebi. The 100 mg daily does have at or ones the level of placebi. The 100 mg daily does have a tot ones of certain tensors pealm (10%) side effects associated with the placebi. The 100 mg daily does have a tot one of certain tensors to 200 mg of amantadine hydrochloride daily because of 10% or often tracicities.

Pediatric Parishest 1 yts 6 mg yar of gar (the total daily does louid be calculated on the basis of 20 of mg/b (14 to 18 mg/b/daily, but not to exceed 150 mg per day.

19 yes, to 12 yes of age 17 he total daily does in 200 mg of any of the daily does in the production population. Therefore, there are no dath with do internocitation that the oos is as effective as or is selfer. The conclusion of the production of

Amandarie hydrochloride stoud be confinued dayly for at least 10 days following a known oppour. If amandarie hydrochloride is used chemopophyladecally in conjunction with inschealed influenza. A virux vaccine until protechee artibody responses develop, then it should be administrated for 20 4 wheels after the vaccine has been pleen. When inschefaled influenza. A virux vaccine is unavailable or confrandeated, amandarie hydrochloride should be administrated by the duration of down influenza. A in the community because of repeated to a finite development of the confrance of 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.

Treatment of influenza A virus ilness 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.

Disage for Parkinsanism:

Disage for Parkinsanism:

Adult The susual doce of annahatine hydrochloride is 100 mg lwice a day when used alone.

Amantatine hydrochloride has an onset of action useally within Adoburus.

The initial disace of annahatine hydrochloride 100 mg daily from the Markinson drugs.

Anter one to several weeks of 100 mg daily flowes of other antiparkinson drugs.

After one to several weeks of 100 mg daily, the does may be increased to 100 mg lwice ally, the does may be increased to 100 mg lwice ally, the does may be increased to 100 mg lwice ally. Occasionally, patients whose responses are not optimal with amantatine hydrochloride at 200 mg daily may benefit from an increase up to 400 mg daily in divided doses. However, such patients should be supervised dosely by their physicians.

Planets inially deriving benefit from annathatine hydrochlotide not uncommonly experient as fails, and offerboleness after a few months. Benefit may be regained by increasing the dis 0.000 ms glash. Alternatively, temporary decontinuation of annathatine phytrochlotide for several weeks, followed by entitlation of the drug, may result in regaining benefit in some patients. A decision to use other artifipations drugs may be recessary.

Desage for Concomitant Therapy: Some patients who do not respond to antificiolinerapic artification drugs may respond to amandatine lydrochloride.

When annabatine hydrochloride or antichatine lydrochloride, and the manabatine hydrochloride or antichatinergo antignation drugs are each used with marginal benefit, concomitant use may produce additional benefit.

When annabatine hydrochloride and leodopa are initiated concurrently, the patient can onlith rapid therapatic benefits. A manabatine hydrochloride should be held constant at 100 mg dally or wine daily while the daily dose of leodopa as gradually increased to optimal benefit.

When amentatine hydrochtoride is added to optimal well-balerated disses of levodopa, additional benefit may result, indicting smoothing out the fluctuations in improvement with sometimes occur in patients on levodopa denne. Patients who require a reduction in their usual dose of levodopa because of iderespinent of side effects may possibly regain lost. Adult: The usual dose of amantadine hydrochloride is 100 mg twice a day, Occasionally, patients whose responses are not optimal with amantadine hydrochloride at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.

Renal Function: Inine clearance, the following dosage adjustments are recommended

MOTORY

CREATININE CLEARANCE (mL/min/1.73m²) 30 to 50 15 to 29 200 mg 1st day followed by 100 mg on alternate days 200 mg 1st day and 100 mg each day thereafter AMANTADINE HYDROCHLORIDE DOSAGE

NeW SUPPLIE :
MEW SUPPLIE :
Marchard Hydrochloride Ord Solution, USP 50 mg/5 mL is a coloriess to pale yellow, florablem in the coloridation available in:
Targetern, "Resource on all outboard available in:
10 mL unit does outpin in seps of 10 (MDC 0116-4010-10)
1 PmL (473 mL) bodies (MDC 0116-4010-16) nded dosage for patients on hemodialysis is 200 mg every 7 days.

<u>15</u>

200 mg every 7 days

Store at 20° to 25°C (68° to 77° L), excursions permitted to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature]. KEEP TIGHTLY CLOSED in a tight container as defined in the USP, with a child-resistant closure

1W.W. Wilson and A.H. Rajput, Amantadine-Dyazide 129:974-975, 1983. REFERENCES Interaction, Can. Med. Assoc. J.

3C.D. Berkowitz, J. Pediatr. 95:144, 1979. 2D.F. Casey, N. Engl. J. Med. 298:516, 1978

REV. 08-24

Amantadine 10mL Lid

UNIT DOSE Delivers 10 mL NDC 0116-4010-10 Amantadine Hydrochloride Oral Solution USP 100 mg per 10 mL



Rx Only FOR INSTITUTIONAL USE ONLY Xttrium Laboratories, Inc. Mount Prospect IL 60056



Amantadine Hydrochloride Oral Solution USP

50 mg/5 mL



There appears to be a relationship between plasma amantadine hydrochloride concentrations and toxolary. As concentration increases, toxicity seems to be more prevalent, however, absorble values of amantadine hydrochloride concentrations associated with adverse effects have not been fully defined.

A mantadine hydrochloride plasmanochleride were determined in 24 normal adult male volunteers after the oral administration of a single amantadine hydrochloride of the concentration was a second of the concentration was concentration and the concentration of the concentration of the concentration was 3.3 ± 1.5 hours (large 0.18 to 3.2 μy/mL). The time to peak concentration was 3.3 ± 1.5 hours (large 0.14 to 0.62 L/m/s). The laft-fie was 17 ± 4 hours (mayer 10 to 5 hours), I near adults a mantadine hydrochloride plasma half-life has averaged 16 ± 6 hours (range: 9 to 31 hours) in 19 healthy volunteers.

Amantadine Hydrochloride Oral Solution USP 50 mg/5 mL

DESCRIPTION Amantadine hydrochloride, USP is designated generically as amantadine Amantadine hydrochloride.

Amantadine hydrochloride has pharmacological actions as both an anti-Parkinsor and an antiviral drug.

Pharmacodynamics
Pharmacodynamics
Mechanism of Jadian; Antiviral: The mechanism by which amentedine
hydrochloride exerts its antiviral activity is not clearly understood. It appears to
mainly prevent the release of infectious viral manufactured actif into the host cell by
interlaining with the fundon of the framework and of the viral M2 by
protein. In certain cases, amental dire hydrochloride is also known to prevent viru
sessenbly during virus epiclaction. It does not appear to interfere with the
immunogenicity of inactivated influenza A virus feaccine.

Artiviral Activity. Amantalina ilydrochhoride inhibits the replication of influenca Artiviral Activity. Amantalina ilydrochhoride inhibits the replication of influenca Avinus sodates from each of the subtypes, i.e., IHIVI, IHIX and IHIXI. It has very little or no activity against influencal at vinus solates, A quantitative relicionship between the *in vitro* susceptibility of influenza A virus to amantadrine by drochhoride required to inhibit by 150% the growth of virus (IED.) of insuese culture vary greatly from 0.1 µg/ml. to 25.0 µg/ml. 10 pending upon the assay protocol used, size of virus in occuloum, isolates of influenza A virus strains seteled, and the cell type used. Host cells in itsuse culture readly toleraded amantadrine hydrochoride have been isolated from pojetemic states in areas where adamantance influenza A virus been isolated from pojetemic states in areas where adamantance eleviratives are being used. Influenza Viruses with reduced in vitro sensitivity of influenza A virus states to mantadrine hydrochoride in the policy of the cell representation of amantadrine hydrochoride in the treatment of Parkinson's cliences and fundamental virus and the cell representation of the policy of the cell representation of the policy influenza in the policy of the p

internal amendation with controlled interactors ranged from 0.2 to 0.3 Lhn/flig after the definitionation of singli 0.25 mg introvenous doses of amantadine by direct birds of 5 mg/l 0.25 mg introvenous doses of amantadine by direct birds of 5 mg/l 0.25 mg introvenous doses of amantadine by direct birds of 5 mg/l 0.25 mg introvenous doses of amantadine by direct birds of 5 mg/l 0.25 mg introvenous doses of amantadine by direct birds of 5 mg/l 0.25 mg introvenous administration of 5 mg/l 0.25 mg/l 0.23 mg/l 0.25 mg/l 0.25

Patients receiving amentadine hydrochloride who note central nervous system effects or burning of vision should be cattinised against driving or working in shaudness where delirenses and adequate motor coordination are important. Other: Patients with a history of congestive heart failure or pepipheral edema should be followed loosely as there are patients who developed congestive heart failure while receiving amentadine hydrochloride.

PRECAUTIONS

PRECAUTIONS

Amentacine by dochlaride should not be discontinued abruptly in patients with Parkinson's disease since a lew patients have experienced in parkinsonian crise, i.e., a sudden marked cinized delerioristich, when this inedication was uddenly discoped. The dose of articiplineigh drugs or on a markatine by dinochlaride abrupted be enduced if attropine-like effects appear when these drugs are used concurrently. Abrupt discontinuation may also precipitate delirum, sightafon, debestors, indiconations, paramotif seadion, stupor, arrively, depression and durinos specifi.

Neurolephic Mali grant Syndrome (NMS): Sporadic cases of possible Neurolephic Malignant Syndrome (NMS) have been reported in association with dose reduction or withdrawal of amandatine hydrochlorids therapy. Interiore, galents should be observed carefully when the dosage of amandatine hydrochlorids is reduced abruptly or discontinued, especially if the patient is receiving neurolephics.

wikis is a uncommon but life-threatening syndrome characterized by faver or hyperthermic neurologic findings including muscle rigidity, involuntary hyperthermic neurologic findings including muscle rigidity, involuntary hyperedirectory and the such as authorized consciousness; media status charques other disturbances such as authorized operations, and horsesed serum impolibrim.

The early diagnost of this condition is important for the appropriate management of these patients. Considering Wikis as a possible diagnosis and ruling out other activities patients. Considering Wikis as a possible diagnosis and ruling out other activities patients. Considering Wikis as a possible diagnosis include owner and the supportant of these patients. Considering Wikis as a possible diagnosis include central and thorized protections of the chiral presentation includes both sorious medical lifess and unreaded or inadequately treated extrayyramided sign and symptoms (ES). Other important considerations in the officeration diagnosis include central arthrochiergic incursity heat stroke, drug fever and primary central intervous system (MS) pathodogs.

18 The management of MIKS should include: 1) intensive symptomatic treatment and medical mortitoring, and 2) treatment of any concomitant serious medical problems for which specific resembness are advantable. Operating appoints, such as bromortytine, and muscle relaxants, such as dambdene are often used in the treatment of MIKS, however, their effectiveness has not been demonstrated in the controlled studies.

Deaths due to drag occumulation (owerdoes) have been reported in patients with beaths due to drag occumulation (owerdoes) and the patients with renal impairment, who were prescribed higher than recommended doese of annationdies byto-childred for their lessel of treat function (see DOSAGE AND ADMINISTRATION): Desage of impairer Renal Function and OPERDOSAGE).

Sincide Attempts: Suicide attempts, some of which have been related in patients treated with an antaline hydrochridre, many of whom reported in patients the read with an antaline hydrochridre, many of whom reported in patients with a statistic health of the prophylaxis. The incidence of suicide attempts and suicidal relations have been reported in patients with and without prior history of psychiatric liness. Annation in hydrochridre with and without prior history of psychiatric liness. Annation of hydrochridred with and without prior history of psychiatric liness. Annation of hydrochridred by the control of patients with an antalia problems in patients with a history of psychiatric disorders or substance abuse. Retents who attempts suicide may exhibit abrornal manufactures, and commonline our incommon. Because of the possibility of serious adverse effects, carbon should be observed when prescribing amantaline hydrochridred by patients bring treated with drugs having CNS effects, or for whom the potential risks outweigh the benefit of treatment.

EXTENSELY of the psychiatric lines and the processible increased seture sorthy.

medications can experience intense urges to gamble, increased sexual urges, makens urges to speint principal to the principal to speint principal to the princi

Melanoms. But Melanoms with Parkinson's disease have Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoms than the general population. Whether the increased risk observed was due to Parkinson's disease or other fladors, such as drugs used to treat Parkinson's disease, is

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using amentatine with doctorate for any indication, bushly periodic sain examinations should be performed by appropriately qualified findiviousle (e.g., demaddogists).

Other: The does of amentatine hydrochloride may need create lad algustment in patients with congestive heart failure, perpineral edema, or orthosizate any performance of the patients with a strong stream of the performance of the patients with a strong when a performance or orthosizate layoutension. Care as found be accorded when administering amentatine hydrochloride by patients with a history of recurrent exemination random patients with pophosis or severe psychonaurosis not controlled by chemotherapeutic agents.

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. Amantadine hydrochloride has not been shown to prevent such complications. Information for Patients: Patients should be advised of the following information:

improve. Avoid excessive alcohol usage, since it may increase the potential for CNS effects such as dizzness, confusion, lightheadedness and orthostatic hypotension. Blurry vision and/or impaired mental acuity may occur. Gradually increase physical activity as the symptoms of Parkinson's disease

Avoid getting up suddenly from a sitting or lying position. If dizziness or lightheadothess occurs, notify physician. Notify physician if modification lensifications, swelling of extremities, difficulty urinating and/or shortness of breath occur.

Do not take more medication than prescribed because of the risk of overdose. If there is no improvement in a few days, or if medication appears less effective after a few weeks, discuss with a physician.

Consult physician before discominuing medication. Seek medical attention immediately if it is suspected that an overdose of medication has been taken. Drug Interactions: Careful observation is required when amantadine hydrochloride is administered concurrently with central nervous system shmulants.

Agerts with anticholinergic properties may potentiate the anticholinergic-like a effects of an antiatine hydrochorduc. Coadministration of thicridazine has been reported to worsen the terrior in elderly patients with Parkinson's disease, however, it is not known if other plenofinazines produce a similar resporse.

Coechmieration of trianteered by deciliprothication tabled in a higher plasma amentadine hydrochlorida forcementation in a 61-year-old man receiving amentadine hydrochlorida 100 mg (100 for Parkinson's disease.) It is not forcem which of the composition of included drugs trainter-energing-drugold-enrichted combibated to the doservation of firelated drugs trainter-energing-drugold-enrichted combibated to the doservation of firelated drugs

Coadministration of quinine or quinitine with amartatine hydrochloride was shown to reduce the renal clearance of amantatine by docthoride by about 30%. The concurrent use of amantatine hydrochloride with like attenuated influenza vaccine (LMV) intranasal has not been a valuated. However, because of the potential for interference between those products, LMV should not be administered within 2 weeks before or 48 hours after administration of amantation by prochoride unless medically indicated. The concern about possible interference arises from the potential for antiviral drugs to inhibit replication of live vaccine evins. The latert inchtrated influenza vaccine evins. The latert individual influenza vaccine can be administered at any time reliative to use of amantation by drochloride.

Carcinegenesis, Mutagenesis: Long-term in viro animal studies designed to evaluate in the carcinogenic potential of anauthatine hydrochloride have not been evaluate in the carcinogenic potential of anauthatine, amendating hydrochloride for the date of the carcinogenic general carcinogenic production of the carcinogenic production of the carcinogenic production of the carcinogenic political production of the carcinogenic political political production of the carcinogenic political political production at the carcinogenic political political production at the carcinogenic political political production at the carcinogenic political production at the carcinogenic political political production at the carcinogenic political political production at the carcinogenic political political production and production at the carcinogenic political political political production and production at the carcinogenic political political

Impairment of Fertility: The effect of amentadine hydrochloride on fertility has not been adequately lessed, that is, in a study conducted under Good Laboratory Pacifice (GLP) and according to current recommended methodology. In a three filler, non-GLP percolucion study in rate, amentadine hydrochloride at a dose of 22 mg/lay (day (legal to the mearcium recommended human dose on a mg/m² 523 gd/ga/ (day feed to the mearcium recommended human dose on a mg/m² basis) administered to both males and females slightly im paried farfility. There

were no effects on fertility at a dose level of 10 mg/kg/day (or 0.3 times the maximum recommended human dose on a mg/m² basis); intermediate doses were not tested.

Failed fertility has been reported during human in vitro fertilization (IVF) when sperm donor ingested amantadine hydrochloride 2 weeks prior to, and during IVF cycle.

Pregnancy:

Predisonic Effects: The effect of anantation bytorchloride on embryostal and participants (Effects: The effect of anantation bytorchloride on embryostal and participants (Effects: The effects of the effec

It is desired to the second of the second of

ADVERSE REACTIONS
The adverse reactions reported most frequently at the recommended dose of The adverse reactions reported most frequently at the recommended dose of annahed the hydrochloride (5 to 10%) are; nausea, dizziness (lightheadedness), and recommia.

Less frequently (1 to 5%) reported adverse reactions are: depression, anniely and irritability, hallucinations; confusion; annoradia, dry mouth constpation, astroit, indeo reloularis; perpited all elema, orflossistic hypotension, headlarie somnoience, nervousness, dream admormatily, agitation, dry nose, fearmas and fatigue.

Infrequently (0.1 to 1%) occurring adverse reactions are: congestive heart failure, populosis, unrary relation, depines, skin rast, vorniting, weakness, sturred speech, euploriat, finking advormatily, amesiat, hypothesiat, hypothesion, decreased libido, and visual disturbance, including punctate subeptihelial or other comed opacity, corneal edema, decreased visual acuity, sensitivity to light, and optic nerve palay.

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

Other adverse reactions reported during postmarketing experience with amantadine hydrochloride usage include:

Nervous System/Psychiatric: coma, stupor, delirium, hypokiņesia, hypertonia, debisions, aggressive bietavior, pararoid reaction, mario: reaction, molumtary muscle confractions, gait abnormatifies, paresthesia, Etc change, and ot ennor. Atrupt discontinuation may also precipitate delirium, agitation, debissions, halucinations, paramoid reaction, stupor, arrively, depression and slurred speech; Cardiovascular: cardioc arrest arrhythmias including malignant arrhythmias; hypotension, and ladhycardia;

Respiratory: acute respiratory failure, pulmonary edema, and tachypnea;

Hematologic: leukocytosis and agranulocytosis; Gastrointestinal: dysphagia;

Skin and Appendages: pruritus and diaphoresis; Special Senses: keratitis and mydriasis;

Miscellaneous: neuroleptic malignant syndrome (see WARNNGS), allergic reactions including statephylactic descitors, sedema, and fever;

Laboratory Test-lewlated: CPK, EBM, serum creatinine, alkaline phosphatase, LDH, bilirobin, GGT, SGOT, and SGPT.

OVERDOSAGE

Deaths have been reported from overdose with amantacine hydrochobride. The lowest reported earlie what dose was 1 gram. Because some patients have attempted suizide by overdosing with amantacine hydrocholical prescriptions should be written for the smallest quantity consistent with good patient meanagement.

Central nervous system effects that have been reported include insomnia.

Central nervous system effects that have been reported include insomnia.

Central nervous system effects that have been reported include include in an analysis of the process of the proce

Pediatric Patients: 1 yr. to 9 yrs. of age: The total daily close should be calculated on the basis of 2 to 4 myllblagy (4.4 to 8.8 myllodgy), but not to exceed 150 mp per day.

9 yrs. to 12 yrs. of age: The 100 mg daily dose is 200 mg given as two teaspoonfuls of prediator operations and agriculture of the 100 mg daily dose has not been studied in this pediatric opopulation. Therefore, there are no data which demonstrate that this dose is as effective as or is safer than the 200 mg daily dose in this patient opopulation.

The initial dose of amantadine hydrochloride is 100 mg daily for patients with serious associated medical filesses or who are receiving high doses of other antipations of utgs, that one to several weeks at 100 mg once daily, the dose may be increased to 100 mg through the dose may be increased to 100 mg through the dose may be increased.

xicity may be attributable to the anticholinergic effects of amantadire loride. Drug overdose has resulted in cardiac, respiratory, renal or centra system toxicity. Cardiac dysfunction includes arrhythmia, tachycardia Occasionally, patients whose responses are not optimal with amantadine hydrochloride at 200 mg daily may benefit from an increase up to 400 mg daily in

Pulmonary edema and respiratory distress (including adult s syndrome — ARDS) have been reported; renal dysfunction d BUN, decreased creatinine clearance and renal insufficiency

The blood electrolytes, urine pH and urinary output should be monitored. If there is no record of recent voiding, catheterization should be done.

DOSA GE AND ADMINISTRATION
The dose of amantatine hydrochloride may need reduction in patients with The dose of amantatine hydrochloride may need reduction in patients with congestive heart failure, perpheral edema, orthostatic hypotension, or impaired renal function (see Dosage for Impaired Renal Function).

Desage for Prophylaxis and Treatment of Uncomplicated Influenza A Virus Illness:
Illness:
Adult: The adult daily dosage of amantadine hydrochloride is 200 mg (four teaspoontible of oral solution) as a single daily dose. The daily dosage may be split into work teaspoontible of oral solution whose a day. If central nervous system effects develop in once-a-day dosage, a split dosage schedule may reduce such completives.

In peisors 65 years of age or other, the daily dosage of amantatine hydrochloride is 100 mg.

A 100 mg daily dose has a list been shown in experimental challenge studies to be effective as prophylaxis in healthy adults who are not at high thisk for influence-healthed complications, however, it has not been of emoratrated that a 100 mg daily dose been studied in the treatment of cactle influenza liness. In recent chincal flast, the incidence of central enerous system (CNS) side effects associated with the 100 mg daily dose was at or near the level of placebo. The 100 mg dose is recommended for persons who have demonstrated imblerance to 200 mg dose is recommended for persons who have demonstrated imblerance to 200 mg of amantation hydrochloride daily because of CNS or other toxicities.

Prophylactic dosing should be started in anticipation of an influenza Aouthreak and before or after contact with individuals with influenza A virus respiratory tract illness.

Amantadine hydrochloride should be continued daily for at least 10 days following a known exposure. If amantadine hydrochloride is used chemogrophyladically in conjunction with inactivated inherizat A virus vaccine until protective antibody responses day dop, then it should be administered for 2 to 4 weeks after the vaccine has been given When inactivated influenza A virus vaccine is unavailable or contraindicated, amantadine hydrochloride should be administered for the duration of known influenza A in the community because of repeated and unknown exposure.

Treatment of influenza A virus fliness should be stated as soon as possible, preferably within, 21 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.

Dosage for Parkinsonism: Adult: The usual dose of amantadine hydrochloride is 100 mg twice a day when used alone. Amantadine hydrochloride has an orset of action usually within 48

divided doss. However, such patients should be supervised closely by their physicians.

Patients initially deriving benefit from amantatine hydrochloride not uncommonly experience a fall-off of effectiveness after a few morits. Benefit may be regained by increasing the does to 300 mg daily. Alternatively, temporary glosomituation of amantatine hydrochloride for several weeks, followed by reinitiation of the drug, may result in regaining benefit as some patients. A decision to use other artipartimson drugs may be necessary.

Design for Concomitant Therapy: Some patients who do not respond to anti-bridinergic artiparties or duss may respond to annufadire in fydrochlaride. With children from the first of the concomitant responds to annufadire in fydrochlaride with the patient of an other first patient of a mistal concomitant responsibilities of the series. In when an annufadire in fydrochlaride and levologia are initiated concurrently, the patient can exhibit rapid this appetitic benefits. Amantatine hydrochlaride should be held constant at 100 mg slaily or twice daily while the daily sose of law odopa is gradually increased to optimal benefit.

When an entatine in ydrochlaride is added to optimal well-tolerated doses of levologa additional benefit may result, including amorting out the fluctuations in improvement which sometimes occur in patients on law odopa adone. Patients who require a reduction in their usual dose of levologa because of development of eight of the processor in the control of the control of the fluctuations in improvement which sometimes occur in patients on levologa additional benefit may possibly regain lost benefit with the addition of amantatine hydrochlaride.

Desage for Drug-Induced Extrapyramidal Reactions:
Adult: The usual does of annahadre hydroxlivoride is 100 mg twice a day.
Occasionally, pallarisk whose responses are not optimal with annahadrine hydroxlivoride at 200 mg daily may benefit from an increase up to 300 mg daily in whided doese.

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

IIIIIeIIded.	
CREATININE	AMANTADINE
CLEARANCE	HYDROCHLORIDE
(mL/min/1.73m2)	DOSAGE
30 to 50	200 mg 1st day and
15 to 29	200 mg 1st day
45	200 mg arran, 7 days
10	ZUU IIII evel y / udys

The recommanded dosage for patients on hemothysis is 200 mg every 7 days. HVW SIP PLIED

Amentadine Hydrochloride Oral Solution. USP 50 mg/5 mL is a colorless to pale lyfe wire respicery/flavored oral solution available in:

10 mL unit dose cups in trays of 10 (NIDC 0116-4010-10)

1 Print (47 am.) bottles (NIDC 0116-4010-16)

Store at 201 to 25°C, 68° to 77°F), excursions permitted to 15° to 30°C (SEP 1067-10). Explain USP 106-4010-16)

KEEP TIGHT U'CLOSED

Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).

Rx Only Can. Med. Assoc. J.

IWM Wilson and A.H. Rajput, Amantadine-Dyazide into 129:974-975. 1983. 2D.F. Casey, N. Engl. J. Med. 298-516, 1978. 3C.D. Berkowitz, J. Pediatr. 95:144, 1979. Manufactured by: Manufactured by: Thiu in Laboratoria Dr. 1000 IP Business Center Dr. Manuf Prospect, IL 00056

amantadine solution

Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0116-4010	
Route of Administration	ORAL			

Active Ingredient/Active Moiety				
Ingredient Name	Basis of Strength	Strength		
AMANTADINE HYDROCHLORIDE (UNII: M6Q1EO9TD0) (AMANTADINE - UNII:BF4C9Z1J53)	AMANTADINE HYDROCHLORIDE	50 mg in 5 mL		

Inactive Ingredients				
Ingredient Name	Strength			
METHYLPARABEN (UNII: A218C7H19T)				
SACCHARIN SODIUM (UNII: SB8ZUX40TY)				
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)				
SORBITOL (UNII: 506T60A25R)				
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)				
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)				
PROPYLPARABEN (UNII: Z8IX2SC1OH)				
WATER (UNII: 059QF0KO0R)				

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0116- 4010-16	473 mL in 1 BOTTLE; Type 0: Not a Combination Product	11/05/2024	
2	NDC:0116- 4010-41	100 in 1 CASE	11/05/2024	
2		10 in 1 TRAY		
2	NDC:0116- 4010-10	10 mL in 1 CUP, UNIT-DOSE; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075060	11/05/2024	

Labeler - Xttrium Laboratories, Inc (007470579)

Registrant - Xttrium Laboratories, Inc (007470579)

Establishment					
Name	Address	ID/FEI	Business Operations		
Xttrium Laboratories, Inc.		007470579	manufacture(0116-4010)		

Revised: 11/2024 Xttrium Laboratories, Inc