Amantadine hydrochloride 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.

Amantadine hydrochloride is contraindicated in patients with known hypersensitivity to amantadine hydrochloride or to any of the other ingredients in amantadine hydrochloride.

Available direct or through your authorized wholesaler or distributor.

Amantadine Hydrochloride Oral Solution, USP

NDC # | DESCRIPTION | SIZE | UNIT OF SALE | COMPARE TO | ORANGE BOOK CODE
---|---|---|---|---|---
50383-807-12 | 50 mg/5 mL Raspberry Flavored Syrup Unit-dose Cups | 10 mL | 100 | Symmetrel® by Alliance Pharmaceuticals | AA
50383-807-16 | 50 mg/5 mL Raspberry Flavored Syrup | 473 mL | 1 | Symmetrel® by Alliance Pharmaceuticals | AA

EACH 5 mL CONTAINS:

ACTIVE: Amantadine Hydrochloride 50 mg/5 mL;

PRESERVATIVE: Methylparaben, Propylparaben;

INACTIVES: Artificial Raspberry Flavor, Citric Acid, Purified Water, Sorbitol Solution.

STORAGE: Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature].

To order products call 800-932-5676 or fax 800-943-3694 • www.akorn.com

NOT FOR PRESCRIBING PURPOSES. PLEASE REFER TO PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.
Amantadine hydrochloride is a white or nearly white crystalline powder, freely soluble in water and soluble in alcohol and in chloroform.

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

Amantadine hydrochloride oral solution contains 50 mg of amantadine hydrochloride per 5 mL and has the following inactive ingredients: artificial raspberry flavor, citric acid, methylparaben, propylparaben, purified water, and sorbitol.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Mechanism of Action: Antiviral
The mechanism by which amantadine 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 is also known to prevent virus assembly during virus replication. It has not been shown to possess direct anticholinergic activity.

Antiviral Activity
Amantadine inhibits the replication of influenza A virus isolates of 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 and the clinical response to treatment has not been established in man. Sensitivity test results, expressed as the concentration of amantadine required to inhibit by 50% the growth of virus (ED50) in tissue culture vary greatly (from 0.1 mcg/mL to 25.0 mcg/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 tolerate amantadine up to a concentration of 100 mcg/mL.

Drug Resistance:
Influenza A variants with reduced in vitro sensitivity to amantadine have been isolated from epidemic strains in areas where amantadine derivatives are being used. Influenza virus isolates 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 virus variants to amantadine and the clinical response to treatment has not been established in man.
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 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 ophthalmuria or phlebitis.

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. The parkinsonian syndrome may have 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 severe sweating.

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 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 dysregulation, tachycardia, tachypnea, hyperpyrexia; hypotension; laboratory findings such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin.

The early diagnosis of this condition is important for the clinical 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 illness or drug interactions. 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 to this 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.

Malignoma
Epidemiological studies have shown that patients with Parkinson’s disease have a higher risk (2- to approximately 6-fold higher) for the development of malignant 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 these drugs are used concurrently. Abrupt discontinuation of amantadine hydrochloride should be considered for patients with a history of recurrent ecczematoid rash, or to patients with psychosis or severe psychoneuropsis not controlled by chemotherapeutic agents.

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or 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.

Sudden change in 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, light-headedness, and orthostatic hypotension.

Avoid getting up suddenly from a sitting or lying position. If dizziness or light-headedness 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 potential for overdose. If there is no improvement in a few days, or if medication appears less effective after a few weeks, discuss with 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 that may interact 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 Dyazide (triamterene/hydrochlorothiazide) has been associated with a mean amantadine concentration in a 61-year-old man receiving amantadine hydrochloride, USP 100 mg TID for Parkinson’s disease.1 It is not known which of the components of Dyazide contributed to the observation or if related drugs produce a similar response. Coadministration of quinidine or quinidine with amantadine was shown to reduce the renal clearance of amantadine 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 virus vaccine. Trivalent inactivated influenza vaccine can be administered at any time relative to use of amantadine hydrochloride.
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, photosensitivity, mild extrapyramidal 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, dyspepsia, skin rash, vomiting, weakness, slurred speech, euphoria, thrombocytopenia, abnormalities of vision, hyperkinesia, hypotension, 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: inclusions of convolution, leukopenia, neutropenia, eczematoid dermatitis, ocular and ophthalmic, abnormal attempt, suicide, and suicidal ideation (see WARNINGS).

Other adverse reactions reported during postmarketing experience with amantadine hydrochloride usage include: fever, somnolence, pyrexia, agitation, tremor, headache, dermal rash, pruritus, pruritis, photosensitivity, increased sweating, dyskinesia, nephrotic syndrome, deafness, tinnitus, abnormal vision, vertigo, tachycardia, and cardiac arrhythmias.

Amantadine hydrochloride should be continued daily for at least one to several weeks at 100 mg once daily, the dose may be increased up to 300 mg daily in divided doses. If central nervous system effects develop, the daily dosage may be reduced to 150 mg daily. Occasionally, patients whose responses are not optimal with the addition of amantadine hydrochloride may result in regaining benefit in some patients. A decision to use other antiparkinson drugs may be necessary.

DOSAGE AND ADMINISTRATION

The dose of amantadine hydrochloride, USP 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 teaspoonsful of oral solution as a single daily dose. The daily dosage may be split into two teaspoonsful of oral solution twice a day. If central nervous system effects develop in a patient who responds to a once-a-day dosage, a spill 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 of 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 teaspoonsfuls of oral solution twice a day. The 100 mg daily dose has not been studied in this pediatric population. Therefore, there are no clinical 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 optimum with amantadine hydrochloride at 200 mg daily may benefit from an increase up to 400 mg daily in divided doses. However, such patients should be supervised closely by their physicians.

Patients initially deriving benefit from 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 re-administration 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 used in conjunction with other drugs, the combination of amantadine hydrochloride for several weeks, followed by re-administration of the drug, may result in regaining benefit in some patients. A decision to use other antiparkinson drugs may be necessary.

**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 ingesting large quantities of 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. Drug overdose has resulted in cardiac, respiratory, gastrointestinal, hematologic, and CNS manifestations. Rarely, those patients with congestive heart failure, peripheral edema, orthostatic hypotension, or impaired renal function (see Dosage for Impaired Renal Function).

**Dosage for Drug-Induced Extrapyramidal Reactions**

Amantadine hydrochloride may produce akathisia, dystonia, and akinesia. In rare instances, it may produce choreiform movements. Although the occurrence has been infrequent, akathisia, dystonia, and akinesia can occur when amantadine hydrochloride hydrochloride is used in combination with levodopa in the treatment of parkinsonism.

**REFERENCES**


Dyazide is a registered trademark of GlaxoSmithKline. Manufactured by: HI-TECH PHARMACAL CO., INC. Amityville, NY 11701

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