

Amantadine (Systemic)

Antiviral; antiparkinsonian agent; adamantane derivative.

Class: Adamantanes 8:18.04 (AHFS primary); am800 (VA primary)cn500 (VA primary)

Brands*: Symmetrel®

*also available generically

Uses

Treatment of Seasonal Influenza A Virus Infections

- Symptomatic treatment of uncomplicated respiratory tract illness caused by influenza A virus in adults, adolescents, and children ≥ 1 year of age.
- Emergence of amantadine-resistant influenza virus may decrease effectiveness of the drug.
- CDC issued interim recommendations concerning the use of antiviral agents for the treatment of influenza during the 2009–2010 influenza season. As of October 2009, more than 99% of influenza viruses circulating in the US were the 2009 influenza A (H1N1) virus susceptible to oseltamivir and zanamivir. (See Uses: 2009 Influenza A (H1N1) Virus Infections.) When treatment of influenza illness is indicated and seasonal influenza is suspected, oseltamivir or zanamivir should be used. If viral surveillance indicates that seasonal influenza A (H1N1) resistant to oseltamivir is circulating and treatment is indicated, CDC states zanamivir should be used; oseltamivir in conjunction with rimantadine or amantadine is an alternative.
- CDC recommends that health-care providers review local surveillance data, if available, to determine whether influenza A or B is most likely and which subtype of influenza A (H1N1 or H3N2) is prominent in the community. Use of diagnostic tests to distinguish influenza A and B should be considered.
- CDC recommends that adamantanes (amantadine, rimantadine) *not* be used alone for treatment of *seasonal* influenza in the US until susceptibility to these antiviral agents has been reestablished in circulating influenza A viruses.
- Information regarding influenza surveillance and updated recommendations for treatment of seasonal influenza are available from CDC at <http://www.cdc.gov/flu>.

Prevention of Seasonal Influenza A Virus Infections

- Prophylaxis of signs and symptoms of influenza A infection in adults, adolescents, and children ≥ 1 year of age.
- Emergence of amantadine-resistant influenza virus may decrease effectiveness of the drug.
- Candidates for antiviral prophylaxis should receive the agent most likely to be effective against the influenza virus that caused the outbreak (if known).
- Prophylaxis of *seasonal* influenza A infection as an adjunct to influenza virus vaccine in high-risk individuals who may have a poor antibody response to the vaccine (e.g., HIV-infected patients, hematopoietic stem cell transplant patients).
- Not a substitute for annual vaccination with influenza virus vaccine inactivated or influenza virus vaccine live intranasal. Vaccination is considered the primary means of preventing *seasonal* influenza and its complications; antiviral agents are considered adjuncts for control and prevention. (See Influenza Virus Vaccines under Interactions.)
- Information regarding influenza surveillance and updated recommendations for prevention of seasonal influenza are available from CDC at <http://www.cdc.gov/flu>.

2009 Influenza A (H1N1) Virus Infections

- Beginning in March and April 2009, cases of human infection with 2009 influenza A (H1N1) virus, previously referred to as the novel 2009 influenza A (H1N1) virus or swine-origin influenza A (H1N1) virus, were reported in Mexico and other countries, including the US.
- CDC issued interim recommendations concerning the use of antiviral agents for treatment and prophylaxis of infections caused by the 2009 influenza A (H1N1) virus (<http://www.cdc.gov/h1n1flu/recommendations.htm>).
- To date, isolates of the 2009 influenza A (H1N1) virus have been resistant to amantadine and rimantadine. These drugs are not recommended for treatment or prophylaxis of these infections.
- Recommendations for use of antiviral agents for treatment or prevention of infections caused by the 2009 influenza A (H1N1) may change as additional data become available (e.g., additional antiviral susceptibility data, efficacy data). Consult the CDC website for the most recent information regarding 2009 influenza A (H1N1) infections (<http://www.cdc.gov/h1n1flu/>).

Avian Influenza A Virus Infections

- May be used for treatment or prophylaxis of avian influenza A virus infections† in certain situations.
- Concomitant use of a neuraminidase inhibitor (i.e., oseltamivir) and an adamantane (amantadine, rimantadine) can be considered in a patient with pneumonic disease or clinical progression if local surveillance data indicate the H5N1 virus is known or likely to be susceptible to an adamantane.

- Should not be used alone for treatment of avian influenza A if a neuraminidase inhibitor is available. Usual drug of choice is oseltamivir.

Pandemic Influenza

- Prophylaxis of influenza in a pandemic situation.
- Resistance to adamantanes (amantadine, rimantadine) may limit their usefulness in a pandemic; the drugs should *not* be used for treatment, but may be considered for prophylaxis if the pandemic strain is susceptible. Because of a lower incidence of adverse effects, rimantadine may be preferred over amantadine for such prophylaxis.
- On June 11, 2009, the WHO declared the first global influenza pandemic in 41 years occurring and issued a phase 6 pandemic alert regarding 2009 influenza A (H1N1). A phase 6 pandemic is characterized by human-to-human spread of an animal or human-animal reassortant virus and sustained community level outbreaks of the virus in at least 2 countries in a single WHO region and sustained community level outbreaks in at least one other country in a different WHO region.

Parkinsonian Syndrome and Drug-induced Extrapyramidal Effects

- Symptomatic treatment of parkinsonian syndrome including postencephalitic, idiopathic, arteriosclerotic types and for the relief of parkinsonian signs and symptoms of carbon monoxide poisoning. Less effective than levodopa.
- Symptomatic treatment of antipsychotic-induced extrapyramidal effects.

Dosage and Administration

Administration

Oral Administration

Administer orally.

Treatment or prophylaxis of influenza: Given as a single daily dose or in 2 equally divided doses (may minimize adverse CNS effects).

Parkinsonian syndrome and drug-induced extrapyramidal effects: Usually administered twice daily.

If insomnia occurs, the last dose should be taken several hours before bedtime.

Dosage

Available as amantadine hydrochloride; dosage expressed in terms of amantadine hydrochloride.

Usual dosage may need to be reduced in patients with congestive heart failure, peripheral edema, orthostatic hypotension, or impaired renal function.

Pediatric Patients

Treatment of Seasonal Influenza A Virus Infections

Oral: Children 1–9 years of age: 4.4–8.8 mg/kg (maximum 150 mg) daily recommended by manufacturer. AAP recommends 5 mg/kg (maximum 150 mg) daily in 2 divided doses.

Children 9–12 years of age: 100 mg twice daily recommended by manufacturer.

Children ≥ 10 years of age: AAP recommends 5 mg/kg daily in 2 divided doses in those weighing < 40 kg or 200 mg daily in 2 divided doses in those weighing ≥ 40 kg.

Children and adolescents ≥ 12 years of age: 200 mg once daily or 100 mg twice daily recommended by manufacturer.

Initiate amantadine treatment as soon as possible, preferably within 24–48 hours after onset of symptoms, and continue for up to 5 days or 24–48 hours after symptoms disappear.

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Children and adolescents ≥ 12 years of age: 200 mg once daily or 100 mg twice daily recommended by manufacturer.

Alternatively, AAP states children weighing > 20 kg can receive 100 mg daily.

Individualize duration of prophylaxis. For maximum effectiveness, must be taken every day during influenza activity in the community.

For prophylaxis in conjunction with influenza virus vaccine, amantadine should be administered for 2–4 weeks after vaccine administration. Children < 9 years of age receiving influenza virus vaccine for the first time may require amantadine prophylaxis for up to 6 weeks following vaccination or until 2 weeks after the second dose of vaccine.

Adults

Treatment of Seasonal Influenza A Virus Infections

Oral: 200 mg once daily or 100 mg twice daily.

Dosage may be decreased to 100 mg daily in those who experience CNS or other toxicities with 200 mg daily; relative efficacy of lower dosage not elucidated.

Initiate amantadine treatment as soon as possible, preferably within 24–48 hours after onset of symptoms, and continue for up to 5 days or 24–48 hours after symptoms disappear.

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For prophylaxis in conjunction with influenza virus vaccine, amantadine should be administered for 2–4 weeks after vaccine administration.

Parkinsonian Syndrome and Drug-induced Extrapyramidal Effects

Oral: 100 mg twice daily.

Patients with serious illness or receiving other antiparkinsonian drugs: 100 mg once daily for ≥ 1 week, then increase to 100 mg twice daily if necessary.

Dosage can be increased to 400 mg daily in divided doses in patients with parkinsonian syndrome.

Dosage can be increased to 300 mg daily in divided doses in patients with drug-induced extrapyramidal reactions.

Prescribing Limits

Pediatric Patients

Treatment or Prevention of Seasonal Influenza A Virus Infections

Oral: Children 1–9 years of age: Maximum 150 mg daily.

Special Populations

Renal Impairment

Dosage in Adults with Renal Impairment

Cl_{cr} (mL/minute)	Dosage
30–50	200 mg on first day, then 100 mg daily
15–29	200 mg on first day, then 100 mg every other day
<15	200 mg every 7 days
Hemodialysis patients	200 mg every 7 days

Geriatric Patients

100 mg daily for treatment or prophylaxis of influenza A virus infection in those ≥ 65 years of age. Dosage may need to be further reduced in some patients.

Cautions

Contraindications

- Known hypersensitivity to amantadine or any ingredient in the formulation.

Warnings/Precautions

Warnings

Acute Toxicity and Suicide Risk

Fatalities reported following overdosage. Overdosage has resulted in cardiac (arrhythmia, tachycardia, hypertension), respiratory, renal, or CNS toxicity; may be related to anticholinergic effects of the drug.

Suicide attempts (including some fatalities) reported rarely; many patients received short courses of the drug for influenza prophylaxis or treatment.

Suicide ideation or attempts reported in patients with or without a prior history of psychiatric disorders. Amantadine can exacerbate mental status in patients with a history of psychiatric disorders or substance abuse. Patients with suicidal tendencies may exhibit abnormal mental states including disorientation, confusion, depression, personality changes, agitation, aggressive behavior, hallucinations, paranoia, other psychotic reactions, somnolence, or insomnia.

Use with caution in patients with uncontrolled psychosis or severe psychoneurosis.

Lowest reported lethal dose is 1 g. Prescriptions should be written for smallest quantity consistent with good patient management.

CNS Effects

Patients with a history of seizure disorders should be observed closely for possible increased seizure activity.

Cardiovascular Effects

CHF reported; monitor patients with a history of CHF or peripheral edema. Dosage adjustment may be needed.

Ocular Effects

Amantadine may cause mydriasis; the drug should not be used in patients with untreated angle-closure glaucoma.

Sensitivity Reactions

Allergic reactions, including anaphylactic reaction, rash, eczematoid dermatitis, photosensitization, pruritus, and diaphoresis, reported rarely.

Use with caution in patients with recurrent eczematoid dermatitis.

General Precautions

Abrupt Withdrawal of Amantadine

Do not abruptly discontinue amantadine in patients with parkinsonian syndrome; some patients have developed parkinsonian crises after abrupt discontinuance of the drug. Abrupt discontinuance also may precipitate delirium, agitation, delusions, hallucinations, paranoid reaction, stupor, anxiety, depression, and slurred speech.

Neuroleptic Malignant Syndrome

Possible neuroleptic malignant syndrome (NMS) reported; associated with dosage reduction or withdrawal of amantadine. Patients should be observed closely when dosage is reduced or the drug discontinued; this precaution is especially important in patients receiving concomitant therapy with an antipsychotic agent.

Melanoma

Epidemiologic studies indicate patients with parkinsonian syndrome have a twofold to sixfold higher risk of developing melanoma than the general population. Unclear whether increased risk is due to parkinsonian syndrome or other factors (e.g., drugs used to treat Parkinson's disease).

Monitor for melanomas frequently and on a regular basis when using amantadine for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Intense Urges

Intense urges (e.g., urge to gamble, increased sexual urges, other intense urges) and inability to control these urges reported in some patients receiving drugs that increase central dopaminergic tone and generally are used for treatment of parkinsonian syndrome, including amantadine. Although causal relationship not established, these urges stopped in some cases when dosage was reduced or the drug discontinued.

Ask patients whether they have developed new or increased gambling urges, sexual urges, or other urges while receiving amantadine; advise them of the importance of reporting such urges. Consider reducing dosage or discontinuing amantadine if a patient develops such urges while receiving the drug.

Other Viral or Bacterial Infections

Not effective for treatment or prophylaxis of viral respiratory tract illnesses other than those due to influenza A virus. (See Uses.)

Serious bacterial infections may present with influenza-like symptoms, coexist with influenza, or occur during influenza. Amantadine does not prevent such complications.

Specific Populations

Pregnancy

Category C.

Lactation

Distributed into milk. Use not recommended.

Pediatric Use

Safety and efficacy not established in neonates or infants <1 year of age.

Increased incidence of seizures reported in children with underlying seizure disorder.

Geriatric Use

Substantially eliminated by the kidneys. Consider age-related decreases in renal function and the potential for concomitant disease when selecting dosage. (See Geriatric Patients under Dosage and Administration.)

Hepatic Impairment

Caution in patients with liver disease. Increased concentrations of liver enzymes reported.

Renal Impairment

Dosage adjustment needed based on degree of renal impairment. (See Renal Impairment under Dosage and Administration.)

Common Adverse Effects

Nausea, dizziness (lightheadedness), insomnia.

Drug Interactions

Specific Drugs

Drug	Interaction	Comments
Alcohol	Potential for increased CNS effects (dizziness, confusion, lightheadedness, orthostatic hypotension)	Avoid excessive usage of alcohol
Anticholinergic agents	Potential for increased adverse anticholinergic and CNS effects	Dosage adjustment of both drugs may be needed

Antihistamines	Potential for increased CNS effects	
Antipsychotic agents	Possible increased risk of NMS (see Neuroleptic Malignant Syndrome under Cautions)	Observe closely if amantadine dosage is reduced or amantadine discontinued
CNS agents	Potential for increased adverse effects	Use with caution
CNS stimulants	Possibility of additive CNS stimulant effects	Caution
Co-triamterzide (triamterene and hydrochlorothiazide)	Possible increased amantadine plasma concentrations	
Co-trimoxazole	Toxic delirium reported in an individual who received co-trimoxazole and amantadine concomitantly	
Influenza virus vaccines	Amantadine does not interfere with the antibody response to influenza virus vaccine inactivated	Can be administered concomitantly with or at any interval before or after influenza virus vaccine inactivated
	Safety and efficacy of concomitant administration of influenza virus vaccine live intranasal and influenza antiviral agents (e.g., amantadine, oseltamivir, rimantadine, zanamivir) have not been studied; potential interference with replication of influenza vaccine viruses	Do not administer influenza virus vaccine live intranasal until at least 48 hours after amantadine is discontinued; do not administer amantadine until at least 2 weeks after administration of the live vaccine
Quinidine or quinine	Potential for a reduction in renal clearance of amantadine	
Thioridazine	Worsened tremor in geriatric patients with parkinsonian syndrome reported	Not known whether a similar effect could occur with other phenothiazines
Urine acidifying drugs	Possible increased elimination of amantadine	

Pharmacokinetics

Absorption

Bioavailability

Well absorbed from GI tract; peak plasma concentrations achieved in 2–4 hours.

Onset

When used for parkinsonian syndrome, onset of action usually within 48 hours.

Plasma Concentrations

Peak plasma concentrations are directly related to amantadine hydrochloride dose up to 200 mg daily; dosages >200 mg daily may result in a greater than proportional increase in peak plasma concentration.

There appears to be a relationship between plasma concentrations of amantadine and toxicity. As concentrations increase, toxicity becomes more prevalent.

Special Populations

Plasma concentrations increased in patients with renal impairment.

Plasma concentrations in geriatric patients receiving a dosage of 100 mg daily approximate those attained in younger adults receiving a dosage of 200 mg daily.

Distribution

Extent

Not fully characterized.

Distributed into nasal secretions, erythrocytes, CSF, and milk.

Plasma Protein Binding

67%.

Elimination

Metabolism

Undergoes *N*-acetylation.

Elimination Route

Principally excreted unchanged in urine by glomerular filtration and tubular secretion; about 5–15% excreted in urine as acetylamantadine.

Only minimally removed by hemodialysis.

Half-life

16 hours (range 9–31 hours).

Special Populations

Half-life prolonged in patients with renal impairment ($Cl_{cr} < 40$ mL/minute). Half-life of 18.5–81.3 hours reported in patients with Cl_{cr} 13.7–43.1 mL/minute; half-life averages 8.3 days (range: 7–10.3 days) in patients undergoing chronic hemodialysis.

Half-life prolonged in healthy geriatric adults. Half-life of 29 hours (range: 20–41 hours) reported in geriatric men 60–76 years of age.

Stability

Storage

Oral

Tablets

25°C (may be exposed to 15–30°C).

Solution

25°C (may be exposed to 15–30°C).

Actions

- Adamantane-derivative (a symmetric tricyclic amine); structurally related to rimantadine.
- Antiviral activity against some strains of influenza A, including some strains of H1N1, H2N2, and H3N2.
- Worldwide incidence of influenza A viruses resistant to adamantanes (amantadine, rimantadine) has increased over the last several years. Most strains of seasonal influenza A (H3N2) circulating in the US during the 2005-2006 influenza season contained the amino acid alteration associated with resistance to amantadine and rimantadine. Data from the 2006-2007 and 2007–2008 influenza seasons indicate that the incidence of resistance to amantadine and rimantadine among influenza A isolates remained high, especially in influenza A (H3N2).
- Almost all seasonal influenza A (H1N1) viruses circulating in the US in late 2008 and early 2009 were susceptible to amantadine and rimantadine; however, all circulating strains of seasonal influenza A (H3N2) tested were resistant to the drugs.
- Some strains of avian influenza A (H5N1) have been susceptible to amantadine; other strains, including influenza A (H5N1) isolated from patients in Asia during 2004 and 2005, have been resistant.
- To date, isolates of 2009 influenza A (H1N1) virus have been resistant to amantadine and rimantadine.
- Inhibits viral replication by interfering with the influenza A virus M2 protein, an integral membrane protein.
- Strains of influenza A virus with reduced susceptibility to amantadine have been produced in vitro and have emerged during therapy with the drug.
- Amantadine-resistant influenza A viruses also are resistant to rimantadine, but may be susceptible to oseltamivir or zanamivir.
- Mechanism of action in treatment of parkinsonian syndrome and drug-induced extrapyramidal reactions unknown. May enhance extracellular concentrations of dopamine at dopaminergic neurons, directly stimulating the dopamine receptor, or increasing sensitivity at receptors.

Advice to Patients

- Risk of CNS effects and blurred vision; use caution when alertness and motor coordination is needed.
- Advise patients with parkinsonian syndrome to gradually increase physical activity as symptoms improve.
- Importance of avoiding excessive alcohol usage.
- Importance of not getting up suddenly from a sitting or lying position; notify clinician if dizziness or lightheadedness occurs.
- Importance of notifying clinician if mood/mental changes, swelling of extremities, difficulty urinating, and/or dyspnea occur.
- Importance of taking amantadine as prescribed; importance of not taking more drug than prescribed. Importance of consulting clinician if there is no improvement after a few days or if drug appears less effective after a few weeks.
- Importance of seeking immediate medical attention for suspected overdose.
- Importance of consulting clinician before discontinuing amantadine.

- Importance of informing clinician if new or increased gambling urges, sexual urges, or other urges occur while receiving amantadine.
- Importance of informing clinician of existing or contemplated concomitant therapy, including prescription and OTC drugs and dietary or herbal products, as well as any concomitant illnesses.
- Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.
- Importance of advising patients of other important precautionary information. (See Cautions.)

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Amantadine Hydrochloride

Oral

Capsules

100 mg*

**Amantadine
Hydrochloride Capsules**

Solution

50 mg/5 mL*

**Amantadine
Hydrochloride Oral
Solution**

Tablets

100 mg*

**Amantadine
Hydrochloride Tablets**

Symmetrel[®], Endo

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
† Use is not currently included in the labeling approved by the US Food and Drug Administration.

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