

Rimantadine (Systemic)

Antiviral; adamantane derivative.

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

Brands*: Flumadine®

*also available generically

Uses

Treatment of Seasonal Influenza A Virus Infections

- Symptomatic treatment of uncomplicated illness caused by influenza A virus.
- Emergence of rimantadine-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 2009 Influenza A (H1N1) Virus Infections under Uses.) 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 the treatment of 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 influenza A infection when timely vaccination with influenza virus vaccine is not feasible, contraindicated, or not available.
- Emergence of rimantadine-resistant influenza virus may decrease effectiveness of the drug.
- CDC recommended that adamantanes (amantadine, rimantadine) *not* be used for prevention of influenza in the US until susceptibility to these antiviral agents has been reestablished in circulating influenza A viruses.
- Candidates for antiviral prophylaxis should receive the agent most likely to be effective against the influenza virus that caused the outbreak (if known).
- 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. 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 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.

Dosage and Administration

Administration

Oral Administration

Administer orally without regard to meals.

Dosages <150 mg daily can be given as a single dose; dosages of 200 mg daily can be given in 2 divided doses. Dividing dosages >100 mg daily into 2 doses may minimize adverse effects.

Dosage

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

Pediatric Patients

Treatment of Seasonal Influenza A Virus Infections

Oral: Children ≥13 years of age†: 100 mg twice daily.

Initiate rimantadine 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.

Prevention of Seasonal Influenza A Virus Infections

Oral: Children 1–9 years of age: 5 mg/kg (maximum 150 mg) once daily.

Children ≥10 years of age: 100 mg twice daily. AAP recommends 5 mg/kg daily in 2 divided doses in those weighing <40 kg or 100 mg twice daily in those weighing ≥40 kg.

Individualize duration of prophylaxis. For maximum effectiveness, must be taken every day during influenza activity in the community. Manufacturer states that safety and efficacy for >6 weeks not established.

For prophylaxis in conjunction with influenza virus vaccine, rimantadine should be administered for 2 weeks after vaccine administration. Children <9 years of age receiving influenza virus vaccine for the first time may require rimantadine 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: 100 mg twice daily.

Initiate rimantadine 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.

Prevention of Seasonal Influenza A Virus Infections

Oral: 100 mg twice daily.

Duration of antiviral prophylaxis should be individualized. For maximum effectiveness, the antiviral agent must be taken every day during influenza activity in the community. Manufacturer states that safety and efficacy for >6 weeks not established.

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

Prescribing Limits

Pediatric Patients

Prevention of Seasonal Influenza A Virus Infections

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

Special Populations

Hepatic Impairment

Treatment or Prevention of Seasonal Influenza A Virus Infections

100 mg daily in patients with severe hepatic impairment.

Renal Impairment

Treatment or Prevention of Seasonal Influenza A Virus Infections

100 mg daily in patients with severe renal impairment ($Cl_{cr} \leq 10$ mL/minute). Further dosage adjustments may be needed.

Geriatric Patients

≥65 years of age: 100 mg daily recommended by the manufacturer; ACIP and others recommend 100 mg daily in those who experienced adverse effects with the usual adult dosage.

Geriatric individuals residing in nursing homes: 100 mg daily.

Cautions

Contraindications

- Known hypersensitivity to adamantane derivatives (rimantadine, amantadine) or any ingredient in the formulation.

Warnings/Precautions

Warnings

CNS Effects

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

General Precautions

Other Viral or Bacterial Infections

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

Serious bacterial infections may present with influenza-like symptoms, coexist with influenza, or occur during influenza.

Prescribing and Dispensing Errors.

Ensure accuracy of prescription; similar spelling of Flumadine[®] (rimantadine) and flutamide may result in errors.

Specific Populations

Pregnancy

Category C.

Lactation

Distributed into milk in rats; adverse effects noted in the offspring of rats given the drug during the perinatal and postnatal period. Use not recommended.

Pediatric Use

Used in children ≥ 1 year of age for prophylaxis of influenza A; has not been evaluated for prophylaxis in infants < 1 year of age.

Safety and efficacy for treatment of influenza A virus infection not established in children. Has been used for the treatment of influenza A infection in children 1–15 years of age; safety and efficacy similar to that in adults.

Geriatric Use

Frequency and severity of adverse effects, including adverse CNS effects, in individuals > 65 years of age receiving rimantadine hydrochloride 100 mg twice daily higher than in younger adults and children.

Consider age-related decreases in renal function when selecting dosage. (See Geriatric Patients under Dosage and Administration.)

Hepatic Impairment

Caution in patients with hepatic impairment. (See Hepatic Impairment under Dosage and Administration.)

Renal Impairment

Caution in patients with renal impairment. (See Renal Impairment under Dosage and Administration.)

Common Adverse Effects

Nausea, insomnia, dizziness.

Drug Interactions

Specific Drugs

Drug	Interaction	Comments
Acetaminophen	Slightly decreased rimantadine peak plasma concentrations and AUC	
Aspirin	Slightly decreased rimantadine peak plasma concentrations and AUC	
Cimetidine	Decreased rimantadine clearance with single dose of cimetidine	Effect of long-term administration not evaluated
Influenza virus vaccines	Rimantadine does not interfere with the antibody response to influenza virus vaccine inactivated Safety and efficacy of concomitant administration of influenza virus vaccine live intranasal and influenza	Can be used concomitantly with influenza virus vaccine inactivated Do not administer influenza virus vaccine live intranasal until at least 48 hours after rimantadine is discontinued; do not administer rimantadine until at least 2 weeks

antiviral agents (e.g., rimantadine, amantadine, oseltamivir, zanamivir) have not been studied; potential interference with replication of influenza vaccine viruses

after administration of the live vaccine

Pharmacokinetics

Absorption

Bioavailability

Well absorbed from GI tract; peak plasma concentrations usually attained within 6 hours.

Commercially available tablets and oral solution are bioequivalent.

Food

Food does not appear to affect absorption.

Distribution

Extent

Not fully characterized. Distributed into nasal secretions.

Crosses the placenta in rats; distributed into milk in rats. Not known whether rimantadine crosses the placenta or is distributed into human milk.

Plasma Protein Binding

40%.

Elimination

Metabolism

Extensively metabolized in the liver.

Elimination Route

Principally excreted in urine (74%) as metabolites and unchanged drug (25%).

Not removed by hemodialysis.

Half-life

25–38 hours in adults and children.

Special Populations

No change in pharmacokinetics in patients with chronic liver disease (mainly stabilized cirrhosis). Clearance reduced and half-life increased twofold in patients with severe hepatic impairment.

In patients with renal impairment, half-life prolonged and clearance decreased.

Stability

Storage

Oral

Tablets

15–30°C.

Oral Solution

15–30°C.

Actions

- Adamantane-derivative (a symmetric tricyclic amine); structurally related to amantadine.
- 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 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 rimantadine; other strains, including influenza A (H5N1) isolated from patients in Asia during 2004 and 2005, have been resistant.
- To date, isolates of the 2009 influenza A (H1N1) virus have been resistant to amantadine and rimantadine.
- 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 rimantadine have been produced in vitro and have emerged during therapy with the drug.
- Rimantadine-resistant influenza A viruses also are resistant to amantadine, but may be susceptible to oseltamivir or zanamivir.

Advice to Patients

- Importance of not getting up suddenly from a sitting or lying position; notify clinician if dizziness or lightheadedness occur.
- 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.

Rimantadine Hydrochloride

Oral

Solution

50 mg/5 mL

Flumadine[®] Syrup, Forest

Tablets, film-coated

100 mg*

Flumadine[®], Forest

Rimantadine Hydrochloride Tablets

*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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