

## Rimantadine Hydrochloride

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

■ Rimantadine hydrochloride, an adamantane derivative, is a synthetic antiviral agent that is structurally related to amantadine and active against influenza A virus.

### Uses

#### ■ Seasonal Influenza A Virus Infections

Rimantadine is used for the *treatment* of influenza A virus infections in adults and for the *prophylaxis* of these infections in adults and children. Rimantadine also has been used for the *treatment* of influenza A virus infection in children†.

Emergence of rimantadine-resistant influenza virus may decrease effectiveness of the drug.

The US Centers for Disease Control and Prevention (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) that 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.

The most appropriate antiviral for the treatment or prevention of influenza is selected based on information regarding the likelihood that the influenza strain is susceptible and the known adverse effects of the drug. The fact that strains of circulating influenza viruses and the antiviral susceptibility of these strains constantly evolves should be considered.

CDC recommends that adamantanes (amantadine, rimantadine) *not* be used alone for the treatment of seasonal influenza in the US or for prevention of *seasonal* influenza in the US until susceptibility to these antiviral agents has been reestablished in circulating influenza A viruses. During the 2005–2006 influenza season, most influenza A (H3N2) strains circulating in the US were resistant to adamantanes (amantadine, rimantadine). Resistance to amantadine and rimantadine among influenza A isolates remained high during the 2006–2007 and 2007–2008 influenza seasons, especially in influenza A (H3N2).

While rimantadine and amantadine generally are comparably effective in the prevention and treatment of influenza A infection caused by susceptible strains, and adverse effects of the drugs are similar, rimantadine may be associated with less frequent and/or severe nervous system effects. Decisions regarding use of rimantadine versus amantadine for the treatment or prevention of influenza A infection caused by susceptible strains should consider the patient's age, weight, renal function; presence of other medical conditions; the potential for drug interactions; and the adverse effect profile and cost of the drug.

There is no clinical evidence that rimantadine is effective for prophylaxis or treatment of other viral diseases, including influenza B virus.

#### **Treatment of Seasonal Influenza A Virus Infections**

When assessing a possible case of influenza, 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. The use of diagnostic tests to distinguish influenza A and B should be considered.

When rimantadine has been used in otherwise healthy adults and children† for symptomatic treatment of uncomplicated seasonal influenza caused by susceptible influenza A virus and administered within 48 hours after the onset of symptoms, the drug has decreased viral shedding and reduced the degree and duration of fever, headache, and respiratory symptoms with a more rapid return to routine daily activities. The drug does not appear to be effective in preventing otologic manifestations of influenza A infection in adults. It is not known whether rimantadine is effective for the symptomatic treatment of this infection in patients whose symptoms have been present for more than 48 hours since most controlled studies evaluating efficacy of the drug only included patients whose symptoms had been present for 48 hours or less. Some evidence suggests that symptomatic improvement during the initial 24 hours of therapy with usual dosages of rimantadine may be somewhat slower than that with amantadine, probably because of pharmacokinetic differences between the drugs.

The appropriate treatment of patients with respiratory illness depends on accurate and timely diagnosis. Early diagnosis of influenza infection can provide the option of using antiviral therapy and reduce inappropriate use of other anti-infective agents. However, some bacterial infections can produce symptoms similar to influenza infection, and the possibility of primary bacterial infection should be considered when making treatment decisions for patients with respiratory illness. Bacterial infection also can occur as a complication of influenza. (For information on differential diagnosis of influenza and influenza-like illnesses, including information on diagnostic tests, see Differential Diagnosis of Influenza and Influenza-like Illnesses under Uses: Treatment of Influenza A Virus Infections, in Amantadine 8:18.04.)

There have been no well-controlled studies to date to determine the efficacy of rimantadine treatment in preventing serious complications of influenza A virus infection (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases). Most studies evaluating efficacy of rimantadine for the treatment of influenza A infections have been performed in otherwise healthy adults and children with uncomplicated influenza; data are limited and inconclusive concerning efficacy of rimantadine for treatment of influenza in individuals at high risk for serious influenza-related complications.

Rimantadine- and amantadine-resistant strains of influenza A virus may appear in up to approximately 33% of patients receiving the drugs for treatment of influenza A infection. Individuals with influenza A infection who are receiving rimantadine or amantadine antiviral treatment may shed strains of the virus that are susceptible to the drugs early in the course of treatment; however, they may shed resistant strains after 2–7 days of therapy. Although most patients recover uneventfully even after resistant strains emerge (because of host immune responses), resistant strains are pathogenic and transmissible and can result in failures of drug prophylaxis in close contacts (e.g., family members, nursing home contacts). Immunocompromised patients may shed resistant strains for prolonged periods. To minimize emergence of resistant strains, rimantadine treatment should be discontinued as soon as clinically warranted, usually after 3–5 days or within 24–48 hours after the disappearance of signs and symptoms. Individuals with influenza-like illness should be separated from and avoid contact with uninfected individuals as much as possible, regardless of whether they are receiving antiviral therapy.

Information regarding influenza surveillance and updated recommendations for treatment of seasonal influenza is available from CDC at <http://www.cdc.gov/flu>.

#### **Prevention of Seasonal Influenza A Virus Infections**

Individuals who are candidates for antiviral prophylaxis should receive the agent most likely to be effective against the influenza virus that caused the outbreak (if known).

Controlled studies in children (1–18 years of age), adults, and geriatric individuals have shown rimantadine to be effective in preventing influenza caused by susceptible type A strains; limited evidence indicates that a protective effect is achieved in up to 90% of individuals who receive the drug throughout an influenza A outbreak. Clinical studies indicate that rimantadine is as effective as amantadine or influenza vaccination in preventing *seasonal* influenza A illness. The protective effect of rimantadine or amantadine and influenza vaccination may be additive. In contrast to results of studies evaluating efficacy when antiviral prophylaxis is given for a season or part of a season, results of studies evaluating antiviral prophylaxis with amantadine or rimantadine after known exposure have not been consistent. While postexposure prophylaxis with rimantadine or amantadine provided protection in families when the index case did not receive antiviral therapy, the drugs did not provide protection from influenza A infection in household contacts when rimantadine or amantadine was used to treat the index case, presumably because of spread of resistant virus within the household.

Annual vaccination with influenza virus vaccine inactivated or influenza virus vaccine live intranasal, as recommended by the US Public Health Service Advisory Committee on Immunization Practices (ACIP), is considered the primary means of preventing *seasonal* influenza and its severe complications. However, prophylaxis with an appropriate antiviral agent is an important adjunct for the control and prevention of influenza. For information on prevention and control of influenza, including CDC guidelines, see Prevention of Influenza A Virus Infections under Uses, in Amantadine 8:18.04.

Information regarding influenza surveillance and updated recommendations for prevention of seasonal influenza is 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. The 2009 influenza A (H1N1) virus appears to be a triple-reassortant swine influenza virus containing genes from human, swine, and avian influenza A viruses. The virus contains a unique combination of gene segments not previously reported among human or swine influenza A in the US or elsewhere.

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) virus may change as additional data become available (e.g., additional antiviral susceptibility data, efficacy data). The CDC website should be consulted for the most recent information regarding case definitions of confirmed, probable, and suspected 2009 influenza A (H1N1) infections and recommendations regarding diagnosis, treatment, and prophylaxis (including outbreak control) of these infections (<http://www.cdc.gov/h1n1flu/>).

#### ■ Avian Influenza A Virus Infections

Adamantane derivatives (amantadine, rimantadine) can be used for the treatment or prophylaxis of avian influenza A virus infections† in certain situations.

The World Health Organization (WHO) recommends use of a neuraminidase inhibitor such as oseltamivir for the treatment of avian influenza A infections. Although many avian influenza A virus strains tested (including the H5N1 strains

isolated from patients in Asia during 2004 and 2005) are resistant to adamantanes (amantadine, rimantadine), most strains have been susceptible to neuraminidase inhibitors (oseltamivir, zanamivir). Some strains from China may be susceptible to adamantanes.

When neuraminidase inhibitors are available, amantadine and rimantadine should *not* be used alone for the treatment of avian influenza A virus infections. However, clinicians can consider treatment with a neuraminidase inhibitor (i.e., oseltamivir) and an adamantane (amantadine, rimantadine) in a patient with pneumonic disease or clinical progression if local surveillance data indicate that the H5N1 virus is known or likely to be susceptible to an adamantane.

For additional information on treatment or prevention of avian influenza A virus infection, see Uses: Avian Influenza A Virus Infections in Oseltamivir 8:18.28.

### ■ Pandemic Influenza

Influenza viruses can cause pandemics, during which rates of illness and death from influenza-related complications can increase dramatically worldwide. Influenza antiviral agents may be important for prophylaxis and treatment if an influenza pandemic occurs. If novel influenza subtypes are involved, the drugs may provide some coverage until a new influenza vaccine active against these strains can be formulated, manufactured, and distributed.

On June 11, 2009, the WHO declared that the first global influenza pandemic in 41 years was 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.

For additional information on pandemic influenza, see Uses: Pandemic Influenza, in Oseltamivir 8:18.28.

## **Dosage and Administration**

### ■ Administration

Rimantadine hydrochloride is administered orally as a single daily dose or in 2 equally divided doses. Dosages of 150 mg or less daily can be given as a single dose, and those of 200 mg daily can be given in 2 divided doses. However, some clinicians recommend that dosages exceeding 100 mg daily be given in 2 divided doses to minimize the risk of adverse effects. Food does not appear to substantially affect GI absorption of rimantadine hydrochloride.

### ■ Dosage

#### **Adult Dosage**

In the *prophylaxis* or symptomatic *treatment* of seasonal influenza A virus infection, the usual dosage of rimantadine hydrochloride for adolescents or adults is 100 mg twice daily. Some clinicians recommend a dosage of 200 mg once daily for the treatment or prevention of seasonal influenza A virus infection in adults.

#### **Geriatric Dosage**

For geriatric individuals residing in nursing homes, the manufacturer, the ACIP, and other clinicians recommend a dosage of 100 mg daily. While further studies are needed to determine the optimal dosage for geriatric individuals who do not reside in nursing homes, the manufacturer recommends a dosage of 100 mg daily for individuals 65 years of age or older. Some clinicians suggest that a dosage of 100 mg daily be considered for any individual 65 years of age or older who experiences adverse effects while receiving 100 mg twice daily.

#### **Pediatric Dosage**

The usual dosage of rimantadine hydrochloride for *prophylaxis* of seasonal influenza A virus infection in children 10 years of age or older is 100 mg twice daily. The American Academy of Pediatrics (AAP) states that children 10 years of age or older who weigh 40 kg or more may receive the drug in a dosage of 100 mg twice daily, but that it may be advisable to administer the drug in a dosage of 5 mg/kg daily given in 2 divided doses to those who weigh less than 40 kg, regardless of age. For children 1–9 years of age, the usual dosage of rimantadine hydrochloride is 5 mg/kg (up to a maximum dosage of 150 mg) once daily.

For the *treatment* of seasonal influenza A virus infection in children 13 years of age or older†, a dosage of 100 mg twice daily is recommended.

#### **Duration of Therapy**

When an influenza A outbreak occurs in institutions that house high-risk individuals, prophylaxis should be started as soon as possible after recognition of the outbreak and continued for at least 2 weeks or until 7–10 days after the end of the outbreak. When rimantadine is used as an adjunct to influenza virus vaccine, the drug usually is administered for 2 weeks after the vaccine is given in order to provide chemoprophylaxis until a protective antibody response develops. Children receiving influenza virus vaccine for the first time may require prophylaxis for up to 6 weeks following vaccination or until 2 weeks after the second dose of vaccine. When vaccination is contraindicated or otherwise not available, rimantadine prophylaxis may be given throughout the period of local influenza A outbreak, which may be as long as 6–12 weeks. Duration of antiviral prophylaxis should be individualized. For maximum effectiveness, the antiviral agent must be taken every day during influenza activity in the community. The manufacturer states that safety and efficacy of rimantadine prophylaxis for longer than 6 weeks have not been established.

In the symptomatic treatment of illness caused by influenza A virus, rimantadine hydrochloride should be administered as soon as possible, preferably within 24–48 hours after the onset of symptoms. Treatment can be continued for up to 5 days or for 24–48 hours after symptoms disappear.

### ■ Dosage in Renal and Hepatic Impairment

Unlike amantadine, which is eliminated unchanged, rimantadine is extensively metabolized in the liver. Because of potential accumulation of rimantadine and/or its metabolites in plasma, the drug should be used with caution and dosage adjusted as appropriate in patients with any degree of hepatic or renal insufficiency. In patients with severe hepatic impairment or renal failure (creatinine clearance less than 10 mL/minute), the manufacturer recommends that dosage of rimantadine hydrochloride be reduced to 100 mg daily. However, the manufacturer cautions that this recommendation is based on pharmacokinetic observations made in single-dose studies and that safety of rimantadine following multiple dosing in individuals with hepatic or renal impairment remains to be established. In addition, dosage adjustment also may be necessary in patients with less severe renal impairment. Because of the potential for accumulation of rimantadine and its metabolites, patients with any degree of renal insufficiency, including geriatric patients, should be monitored for adverse effects and either the dosage should be reduced or the drug discontinued as necessary. Rimantadine is not removed by hemodialysis.

## **Cautions**

Rimantadine generally is well tolerated, although serious adverse effects have been reported rarely. The most frequently reported adverse effects with rimantadine are similar to those observed with amantadine and include adverse CNS and GI effects; however, rimantadine is associated with less frequent and/or severe nervous system effects than amantadine, including in geriatric adults.

Adverse effects associated with rimantadine usually are mild and are reversible upon discontinuance of the drug. In some patients, adverse effects may subside or disappear after the first week despite continued therapy with the drug. However, serious adverse effects also can occur. The incidence of adverse effects (e.g., CNS and GI effects) reported in geriatric patients receiving rimantadine or placebo in clinical studies has been higher than the incidence in younger adults or children. In addition, the incidence of adverse effects (e.g., CNS effects, GI effects) appears to be higher in individuals receiving rimantadine dosages exceeding the recommended dosage.

### ■ Nervous System Effects

Insomnia, nervousness/jitteriness, dizziness/lightheadedness, or impaired concentration has been reported in 2.1–3.4, 1.3–2.1, 0.7–1.9, or 2.1% of patients, respectively, receiving the recommended dosage of rimantadine hydrochloride (200 mg daily) in clinical studies. Such CNS effects generally resolve within 48 hours after discontinuance of the drug. Headache, asthenia, fatigue, or depression occurred in 1.4, 1.4, 1, or 0.7% of patients, respectively, in these studies. Ataxia, somnolence, or agitation has occurred in 0.3–1% of patients receiving rimantadine in clinical studies. Adverse nervous system effects reported in less than 0.3% of patients in clinical studies include gait abnormalities, euphoria, hyperkinesia, tremor, hallucinations, or confusion. Agitation and hypesthesia have occurred in patients receiving rimantadine dosages exceeding the recommended dosage.

Seizures or seizure-like activity has been reported in a few patients with a history of seizure disorder who were receiving rimantadine but whose anticonvulsant therapy had been withdrawn. Seizures also have occurred rarely in nursing home residents receiving rimantadine. While patients with active seizure disorders appear to be at risk of increased frequency of seizures during amantadine therapy, the effect of rimantadine therapy on the incidence of seizures in such individuals has not been fully evaluated.

Adverse CNS effects (e.g., nervousness, anxiety, impaired concentration, lightheadedness) are less common with usual dosages of rimantadine than amantadine, probably in part because of differences in the pharmacokinetics of the drugs. In a 6-week study of daily 200-mg prophylactic doses of rimantadine hydrochloride or amantadine hydrochloride in healthy adults, about 6 or 13% of patients receiving the respective drug discontinued therapy because of adverse CNS effects versus about 4% of those receiving placebo. While neuropsychiatric (e.g., delirium, marked behavioral changes) or psychomotor dysfunction has occurred in patients receiving amantadine, these effects have not been reported in patients receiving rimantadine.

While the type of adverse CNS effects reported in rimantadine-treated geriatric individuals is similar to that in younger adults, these adverse effects occur more frequently in geriatric individuals. In controlled studies in patients 65 years of age or older receiving rimantadine hydrochloride 200 or 400 mg daily or placebo for 1–50 days, CNS effects including dizziness, headache, anxiety, asthenia, and fatigue, occurred up to 2 times more often in geriatric individuals receiving rimantadine than in those receiving placebo. Nursing home residents, a group with many underlying medical problems, may be particularly susceptible to adverse CNS effects.

The more serious adverse events (e.g., marked behavioral changes, delirium, hallucinations, agitation, seizures) of amantadine or rimantadine have been associated with high plasma concentrations of the respective drug and have been observed most often among patients with renal impairment, seizure disorders, or certain psychiatric disorders, and among geriatric patients who received amantadine hydrochloride prophylactic dosages of 200 mg daily. Clinical studies and experience indicate that lower dosages of amantadine in at-risk patients reduce the incidence and severity of these serious adverse effects. The safety of rimantadine in some patient groups (i.e.,

geriatric individuals, those with chronic disease) has not been completely evaluated; however, dosages of 100 mg daily appear to be well tolerated in geriatric adults. Suicide attempts or exacerbation of mental status in patients with a history of psychiatric disorders or substance abuse has been reported in patients receiving amantadine.

### ■ GI Effects

Nausea is one of the most frequent adverse GI effects of rimantadine and has been reported in about 3% of patients receiving the usual dosage (200 mg daily) of the drug. Vomiting, anorexia, dry mouth, or abdominal pain has occurred in 1–2% of patients receiving the drug in the recommended dosage. Adverse GI effects reported in 0.3–1% of patients include diarrhea or dyspepsia. Dysphagia or stomatitis has occurred in patients receiving rimantadine dosages exceeding the recommended dosage. The incidence of adverse GI effects is comparable for rimantadine and amantadine.

Nursing home residents may be particularly susceptible to adverse GI effects of rimantadine or amantadine. In controlled studies in patients 65 years of age or older receiving rimantadine 200 or 400 mg daily or placebo for 1–50 days, adverse GI effects (nausea, vomiting, abdominal pain) occurred at least twice as frequently in geriatric individuals receiving rimantadine compared with the incidence in those receiving placebo. The GI effects appeared to be dose related.

### ■ Other Adverse Effects

Rash, tinnitus, or dyspnea has occurred in 0.3–1% of patients receiving rimantadine. Adverse effects reported in less than 0.3% of patients include bronchospasm, cough, pallor, palpitation, hypertension, cerebrovascular disorder, cardiac failure, pedal edema, heart block, tachycardia, syncope, nonpuerperal lactation, alteration in taste, or parosmia. Increased lacrimation, increased micturition frequency, fever, rigor, diaphoresis, or ocular pain has been reported in patients receiving rimantadine dosages exceeding the recommended dosage.

### ■ Precautions and Contraindications

While the effect of rimantadine therapy on the incidence of seizures in patients with seizure disorders has not been fully evaluated, patients with active seizure disorders appear to be at risk of increased frequency of seizures during amantadine therapy. Therefore, rimantadine-treated patients with a history of epilepsy or other seizures should be observed closely for possible seizure activity. The manufacturer states that rimantadine should be discontinued if seizures develop.

Unlike amantadine, which is eliminated unchanged, rimantadine is extensively metabolized in the liver. Because of potential accumulation of rimantadine and/or its metabolites in plasma, the drug should be used with caution and dosage adjusted as appropriate in patients with hepatic or renal insufficiency. (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Rimantadine- and amantadine-resistant strains of influenza A virus have been observed in some patients receiving the drug for the treatment of influenza A infection. Although most patients recover uneventfully even after resistant strains emerge, resistant strains are transmissible and can result in failures in drug prophylaxis in close contacts. The possibility of transmitting resistant strains should be considered when treating patients in close contact with other individuals at high risk for influenza A infection. Individuals with influenza-like illness should be separated from and avoid contact with uninfected individuals as much as possible, regardless of whether they are receiving antiviral treatment.

Clinicians should consider the possibility of primary or concomitant bacterial infection when making treatment decisions for patients with suspected influenza.

The manufacturer cautions that, because of similarity in spelling between Flumadine<sup>®</sup> (the trade name for rimantadine) and flutamide (an antiandrogen), extra care should be exercised in ensuring the accuracy of the prescription.

Rimantadine is contraindicated in patients with known hypersensitivity to adamantane derivatives (i.e., amantadine, rimantadine).

### ■ Pediatric Precautions

Safety and efficacy of rimantadine in children younger than 1 year of age have not been established.

The manufacturer states that safety and efficacy of rimantadine for the treatment of influenza A virus infection in children have not been established. However, the drug has been used for the treatment of influenza A infection in a limited number of children 1–15 years of age; results of these studies suggest that safety and efficacy of rimantadine are similar to those in adults.

When used in children, rimantadine has caused mild CNS symptoms, which resolve when the drug is discontinued. The incidence of adverse CNS-related effects appears to be lower in individuals receiving rimantadine than in those receiving amantadine.

### ■ Geriatric Precautions

Safety and efficacy of rimantadine have been evaluated in controlled clinical studies in approximately 200 individuals 65 years of age or older. Rimantadine generally is well tolerated in geriatric patients. Although the frequency and severity of adverse effects, including adverse CNS effects, reported in individuals older than 65 years of age at a rimantadine hydrochloride dosage of 100 mg twice daily are higher than those reported in younger adults and children, rimantadine is better tolerated than amantadine at this dosage in geriatric patients.

Geriatric patients may have decreased renal function and because patients with renal impairment may be at increased risk of rimantadine-induced toxicity, patients in this age group should be monitored closely and dosage adjusted accordingly. (See Dosage: Adult Dosage.)

### ■ Mutagenicity and Carcinogenicity

Rimantadine was not mutagenic in several standard assays for mutagenicity.

Animal studies have not been performed to evaluate the carcinogenic potential of rimantadine.

### ■ Pregnancy, Fertility, and Lactation

#### *Pregnancy*

Rimantadine hydrochloride has been reported to be embryotoxic (i.e., increased fetal resorption) in rats when administered in a dosage of 200 mg/kg daily (11 times the recommended human dose based on body surface area); this dose also was associated with several maternal effects including ataxia, tremor, seizures, and substantially reduced weight gain. While developmental abnormality (i.e., change in the ratio of 12 or 13 ribs) was observed in rabbits given rimantadine hydrochloride dosages of 50 mg/kg daily (5 times the recommended human dosage based on body surface area), embryotoxicity was not observed. Reproductive studies in rats given rimantadine hydrochloride dosages of 30, 60, or 120 mg/kg daily (1.7, 3.4, or 6.8 times the recommended human dosage based on body surface area) during the perinatal and postnatal period have shown an increase in pup mortality during the first 2–4 days postpartum in rats given the 120-mg/kg daily dosage, and maternal toxicity during gestation in rats given the 60- or 120-mg/kg daily dosage. There are no adequate and well-controlled studies using rimantadine in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

#### *Fertility*

Decreased fertility has been reported in offspring of female rats given rimantadine hydrochloride 60 or 120 mg/kg daily during the perinatal and postnatal period.

#### *Lactation*

Rimantadine has been associated with adverse effects in offspring of rats given the drug during the perinatal and postnatal period. Therefore, the manufacturer states that rimantadine should not be used in nursing women.

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## Drug Interactions

### ■ Influenza Virus Vaccines

Rimantadine hydrochloride does not interfere with the antibody response to influenza virus vaccine inactivated, and the drug may be given concomitantly with this vaccine.

Safety and efficacy of concomitant use of influenza virus vaccine live intranasal and antiviral agents used for treatment or prevention of influenza (e.g., amantadine, oseltamivir, rimantadine, zanamivir) have not been studied. Because influenza antiviral agents reduce replication of influenza viruses, do not administer influenza virus vaccine live intranasal until at least 48 hours after rimantadine is discontinued and do not administer rimantadine until at least 2 weeks after administration of influenza virus vaccine live intranasal.

### ■ Cimetidine

Administration of a single 100-mg dose of rimantadine 1 hour after initiation of oral cimetidine 300 mg 4 times daily in healthy adults decreased the apparent clearance of rimantadine by 18% compared with administration of cimetidine alone, but this change was not considered clinically important. The effect of long-term administration of rimantadine with cimetidine has not been evaluated to date.

### ■ Acetaminophen

Concomitant administration of rimantadine hydrochloride 100 mg twice daily for 8 days with acetaminophen 650 mg 4 times daily in healthy adults reduced the peak plasma concentration and area under the plasma concentration-time curve (AUC) of rimantadine by 11%.

### ■ Aspirin

Concomitant administration of rimantadine hydrochloride 100 mg twice daily with aspirin 650 mg 4 times daily for 8 days reduced the peak plasma concentration and AUC of rimantadine by 10%.

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## Acute Toxicity

### ■ Pathogenesis

Limited information is available on the acute toxicity of rimantadine.

### ■ Manifestations

Acute overdosage of a related drug, amantadine, has resulted in agitation, hallucinations, cardiac arrhythmia, and death. The possibility that similar effects might occur with rimantadine overdosage should be considered.

### ■ Treatment

If acute overdosage of rimantadine occurs, supportive and symptomatic treatment should be initiated and the patient closely observed. The patient should be observed for seizures. Rimantadine is not removed by hemodialysis.

The manufacturer of rimantadine states that IV administration of physostigmine salicylate has been effective in the management of CNS toxicity caused by amantadine. However, the risks of physostigmine therapy as an antidote should be considered. (See Physostigmine Salicylate 12:04.)

## Mechanism of Action

The exact mechanism of the antiviral activity of rimantadine has not been fully elucidated.

Rimantadine, like amantadine, inhibits viral replication by interfering with the influenza A virus M2 protein, an integral membrane protein. The M2 protein of influenza A functions as an ion channel and is important in at least 2 aspects of virus replication, disassembly of the infecting virus particle and regulation of the ionic environment of the transport pathway. By interfering with the ion channel function of the M2 protein, rimantadine inhibits 2 stages in the replicative cycle of influenza A. Early in the virus reproductive cycle, rimantadine inhibits uncoating of the virus particle, presumably by inhibiting the acid-mediated dissociation of the virion nucleic acid and proteins, which prevents nuclear transport of viral genome material. Rimantadine also prevents viral maturation in some strains of influenza A (e.g., H7 strains) by promoting pH-induced conformational changes in influenza A hemagglutinin during its intracellular transport late in the replicative cycle. Adsorption of the virus to and penetration into cells do not appear to be affected by rimantadine. In addition, rimantadine does not interfere with the synthesis of viral components (e.g., RNA-directed RNA polymerase activity).

Rimantadine treatment of established influenza A infection does not appear to interfere with antibody response to the infection; however, some reduction in local immune responses has been observed in some patients. Because prophylactic use of rimantadine can prevent influenza illness and to a lesser extent subclinical infection, some individuals who take rimantadine can still develop immune responses that may protect them when they are exposed to the same or antigenically related viruses following discontinuance of rimantadine prophylaxis. Rimantadine does not interfere with the immunogenicity of influenza A virus vaccine inactivated. (See Influenza Virus Vaccines under Drug Interactions.)

Rimantadine-mediated increases in lysosomal pH may inhibit virus-induced membrane fusion in enveloped RNA viruses that are susceptible to higher concentrations of rimantadine than those required to inhibit influenza A.

Unlike amantadine, rimantadine does not exhibit antiparkinsonian activity.

## Spectrum

Rimantadine shares the antiviral spectrum of activity of amantadine. Cell culture studies have shown that low concentrations of rimantadine (i.e., less than 1 mcg/mL) produce an inhibitory action against some strains of influenza A, including susceptible strains of H1N1, H2N2, and 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, strains of seasonal influenza A (H3N2) circulating during the 2008-2009 influenza season have been resistant to these drugs. (See Resistance.)

Although some strains of avian influenza A H5N1 may be susceptible to rimantadine in vitro, most avian influenza A virus strains tested (including the H5N1 strains isolated from patients in Asia during 2004 and 2005) are resistant to adamantanes (amantadine, rimantadine).

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. To date, isolates of 2009 influenza A (H1N1) virus have been resistant to amantadine and rimantadine.

In cell culture systems, the 50% inhibitory concentration of rimantadine for influenza A viruses ranges from 4 ng/mL to 20 mcg/mL depending on the assay protocol, size of the virus inoculum, influenza A strain, and the cell type used. By plaque inhibition, the 50% inhibitory concentration of rimantadine or amantadine for influenza A viruses ranges from 0.01 to less than 1 mcg/mL. The precise relationship between in vitro susceptibility of influenza A virus to rimantadine and clinical response to therapy with the drug has not been determined. Results of several in vitro studies indicate that rimantadine is more active on a weight basis than amantadine.

Genetic studies indicate that the amino acid sequence in the transmembrane portion of the M2 protein of influenza A virus influences susceptibility of the virus to rimantadine and amantadine. Single amino acid changes in a critical transmembrane region of the M2 protein are associated with antiviral resistance to the drugs, providing further evidence of the importance of this domain in the protein as a target site for antiviral activity. There is some evidence that susceptibility of certain strains (e.g., H7) may be influenced by gene coding for the viral hemagglutinin.

Rimantadine has little or no activity against influenza B at concentrations that inhibit influenza A. At very high concentrations (10–50 mcg/mL), the drug exhibits some in vitro activity against influenza B and other enveloped viruses (e.g., parainfluenzae, respiratory syncytial virus), but this activity is considered clinically irrelevant because of the relatively high, potentially toxic doses that would be required.

## Resistance

Strains of influenza A resistant to rimantadine have been produced in vitro, and rimantadine-resistant strains have emerged during treatment with the drug. Influenza A with an in vitro EC<sub>50</sub> (concentration of the drug required to produce a 50% reduction of antigenic material) exceeding 1 mcg/mL generally is considered resistant to rimantadine.

Resistance to adamantane-derivative antivirals appears to result from point mutations in the viral RNA segment 7 encoding the M2 protein that leads to amino acid alterations at residue 31 or nearby positions in the transmembrane portion of the M2 protein of the virus.

Although the frequency with which resistant strains emerge and the extent of their transmission have not been elucidated fully, limited evidence suggests that following treatment with rimantadine in immunocompetent patients infected with initially susceptible strains of influenza A, 10–30% will shed rimantadine-resistant virus. Limited information is available on the emergence of drug-resistant influenza A virus in immunocompromised patients receiving rimantadine or amantadine; isolates recovered from immunocompromised patients (adult bone marrow transplant recipients, adults with leukemia) who shed virus for longer than 3 days have been screened for antiviral susceptibility. While initial viral isolates were susceptible to rimantadine or amantadine, subsequent isolates from almost all of the patients were resistant.

The worldwide incidence of influenza A viruses resistant to adamantanes (amantadine, rimantadine) has increased. Results of a study that screened circulating influenza A viruses obtained from various countries between 1994 and 2005 indicated a substantial increase in the percentage of amantadine- and rimantadine-resistant influenza A H3N2 isolates in the US and Asia (China, Hong Kong, Taiwan, South Korea). In Asia, the incidence of such resistance was 1.1% in both 1995 and 2000 and increased to 24.3% in 2003 and 27% in 2004. In the US, the incidence of such resistance was 0.3% in 1995, 1.6% in 2000, and 1.9% in 2004; however, about 15% of influenza A H3N2 strains obtained in the US from October 2004 to March 2005 were resistant to amantadine and rimantadine. 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 indicated that the incidence of resistance to adamantanes among influenza A isolates remained high, especially among influenza A (H3N2). All circulating strains of *seasonal* influenza A (H3N2) tested from the 2008–2009 influenza season have been resistant to amantadine and rimantadine.

While rimantadine-resistant strains appear to be pathogenic and transmissible, there is no evidence that such strains are more virulent or more transmissible than strains that are susceptible to the drug. Resistance has rarely been detected during screening of naturally occurring epidemic strains of influenza A, and most clinical or population-based strains isolated to date are susceptible to rimantadine and amantadine. Resistant strains have been detected in up to about 33% of individuals receiving rimantadine or amantadine for treatment of influenza, and resistant strains also have been isolated from individuals who resided at home or in an institution where other residents were receiving or had recently received rimantadine or amantadine therapy. Rimantadine-resistant strains of influenza A can emerge within 2–3 days of initiating treatment with the drug.

Rimantadine-resistant strains of influenza A are completely cross-resistant to amantadine. Influenza A virus strains resistant to amantadine and rimantadine may be susceptible to oseltamivir or zanamivir.

## Pharmacokinetics

The pharmacokinetics of rimantadine hydrochloride have been studied in children, healthy adults, and geriatric adults. The pharmacokinetics of the drug also have been evaluated in a limited number of patients with renal or hepatic impairment.

The pharmacokinetic profile of rimantadine is characterized by relatively low plasma drug concentrations but high and persistent rimantadine concentrations in respiratory secretions (e.g., nasal secretions), and extensive metabolism in the liver. A correlation between plasma rimantadine concentrations and antiviral activity has not been established, although there is some evidence of a relationship between plasma concentrations and adverse effects, albeit exhibiting considerable interindividual variation.

### ■ Absorption

Rimantadine hydrochloride is well absorbed following oral administration with peak plasma concentrations generally occurring within 6 hours in healthy adults. While the absolute bioavailability of rimantadine has not been determined, relative bioavailability of the drug administered to adults as the commercially available tablets is similar to that achieved following administration of the commercially available oral solution. In one study in healthy adults comparing the oral bioavailability of a single 100-mg dose of the commercially available tablets and solution (syrup) with an aqueous solution of the drug, the tablets and syrup had relative bioavailabilities of 96 and 117%, respectively, but the differences were not considered clinically important. Presence of food in the GI tract does not affect the rate or extent of absorption.

Following oral administration of a single 100-mg dose of rimantadine hydrochloride in healthy adults, peak plasma concentrations averaged 74 ng/mL (range: 45–138 ng/mL). Following oral administration of rimantadine hydrochloride 100 mg twice daily for 10 days in healthy adults 18–43 years of age, peak plasma concentrations averaged 416 ng/mL on day 10 and trough concentrations ranged from 175–422 ng/mL on day 5. Following oral administration of rimantadine hydrochloride 100 mg twice daily for 9.5 days in healthy adults 50–60 years of age (mean creatinine clearance 95 mL/minute), 61–70 years of age (mean creatinine clearance 88 mL/minute), or 71–79 years of age (mean creatinine clearance 79 mL/minute), peak plasma concentrations averaged 417, 401, or 538 ng/mL, respectively, after the last dose on day 10. Trough concentrations averaged 292, 275, or 368 ng/mL, respectively, on day 5 when they had

reached relatively constant values. With multiple dosing, peak plasma concentrations after the last dose were almost 5 times those after the first dose. Results of this study did not reveal substantial age-related differences in the pharmacokinetics of rimantadine; however, geriatric patients frequently have decreased renal function, and peak plasma rimantadine concentration and area under the concentration-time curve (AUC) in individuals 50–79 years of age appear to be related to creatinine clearance. Substantial increases in peak plasma concentrations (i.e., 2- to 4-fold) have been reported in nursing home residents receiving rimantadine. In one study, steady-state plasma concentrations in nursing home residents (68–102 years of age) receiving rimantadine hydrochloride 100 mg twice daily averaged 1159 ng/mL.

Following oral administration of rimantadine hydrochloride 100 mg twice daily in healthy adults, steady-state plasma concentrations are achieved by day 5. AUC values following administration of rimantadine hydrochloride 100 mg twice daily for 10 days in individuals 18–70 years of age are about 30% greater than values predicted from single-dose studies.

Following oral administration of a single 6.6-mg/kg dose of rimantadine hydrochloride in a limited number of children 4–8 years of age, plasma concentrations averaged 657 ng/mL (range: 446–988 ng/mL) at 5–6 hours, and 300 ng/mL (range: 170–424 ng/mL) at 24 hours.

In a limited number of adults with chronic liver disease (i.e., stabilized cirrhosis) receiving a single dose of rimantadine hydrochloride, peak plasma concentrations and AUC values were essentially the same as values in healthy adults. However, AUC values were increased threefold in adults with severe hepatic dysfunction compared with values in healthy adults.

### ■ Distribution

Distribution of rimantadine hydrochloride into body tissues and fluids has not been fully characterized. Following oral administration, rimantadine is distributed into nasal secretions in concentrations 50% higher than plasma concentrations. In one study in adults 51–79 years of age receiving rimantadine hydrochloride 100 mg twice daily for 9.5 days, steady-state trough rimantadine concentration in nasal secretions or plasma averaged 465 or 310 ng/mL, respectively. Rimantadine has been detected in CSF in animals. Rimantadine is about 40% bound to plasma proteins, mainly albumin.

It is not known whether rimantadine crosses the placenta in humans; placental transfer of the drug has been demonstrated in mice. While it is not known whether rimantadine is distributed into human milk, the drug is distributed into milk in rats.

### ■ Elimination

Rimantadine hydrochloride is metabolized extensively in the liver to at least 3 hydroxylated metabolites. These have been designated as conjugated and unconjugated 3-, 4 $\alpha$ -, and 4 $\beta$ -hydroxylated metabolites. A glucuronide conjugate of rimantadine also has been identified. In healthy adults, about 74% of a single 200-mg oral dose was excreted in urine within 72 hours as metabolites and unchanged drug. Less than 25% of an oral dose reportedly is excreted in urine unchanged.

Following oral administration, the plasma elimination half-life of rimantadine averages 25–38 hours in children and adults with normal renal and hepatic function. While the plasma elimination half-life in individuals with chronic liver disease (i.e., stabilized cirrhosis) is not prolonged compared with healthy individuals, the plasma elimination half-life in those with severe liver disease is prolonged 1.6-fold and the apparent clearance is 50% lower compared with healthy individuals. The plasma elimination half-life was increased 1.6-fold (44 versus 28 hours) and apparent clearance decreased 40% in individuals with end-stage renal failure (creatinine clearance 0–10 mL/minute) compared with healthy individuals. In one study in patients with a creatinine clearance of 31–50 or 11–30 mL/minute who received a single 200-mg dose of rimantadine hydrochloride, apparent clearance was reduced 37 or 16%, respectively, and plasma metabolite concentrations were higher than in patients with creatinine clearance values exceeding 50 mL/minute.

Rimantadine is not removed by hemodialysis.

## Chemistry and Stability

### ■ Chemistry

Rimantadine hydrochloride is a synthetic adamantane-derivative (a symmetric tricyclic amine) antiviral agent. Rimantadine is structurally related to amantadine, differing only in the side chain of the 10 carbon ring. While the structure-activity relationship of the adamantanes remains to be determined, the octanol/water coefficient for rimantadine is substantially higher than that for amantadine.

Rimantadine hydrochloride occurs as a white to off-white crystalline powder and has solubilities of 50 mg/mL in water at 20°C. Commercially available rimantadine hydrochloride oral solution occurs as a clear, colorless, raspberry-flavored solution and has a pH of 5.5–7.

### ■ Stability

Commercially available rimantadine hydrochloride tablets and oral solution should be stored in tight, light-resistant containers at 15–30°C.

## 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 (with parabens), Forest

#### Tablets, film-coated

100 mg\*

Flumadine® (with polyethylene glycol), 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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