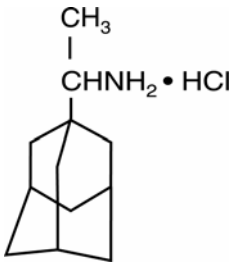
Flumadine® Tablets
(rimantadine hydrochloride tablets)
Flumadine® Syrup
(rimantadine hydrochloride syrup)

Rx only

DESCRIPTION: Flumadine® (rimantadine hydrochloride) is a synthetic antiviral drug available as a 100 mg film-coated tablet and as a syrup for oral administration. Each film-coated tablet contains 100 mg of rimantadine hydrochloride plus hypromellose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, FD&C Yellow No. 6 Lake and FD&C Yellow No. 6. The film coat contains hypromellose and polyethylene glycol. Each teaspoonful (5 mL) of the syrup contains 50 mg of rimantadine hydrochloride in a dye-free, aqueous solution containing citric acid, parabens (methyl and propyl), saccharin sodium, sorbitol and flavors.

Rimantadine hydrochloride is a white to off-white crystalline powder which is freely soluble in water (50 mg/mL at 20°C). Chemically, rimantadine hydrochloride is alpha-methyltricyclo-[3.3.1.1/3.7]decane-1-methanamine hydrochloride, with an empirical formula of C12H21N•HCl, a molecular weight of 215.77 and the following structural formula:



CLINICAL PHARMACOLOGY: *MECHANISM OF ACTION:* The mechanism of action of rimantadine is not fully understood. Rimantadine appears to exert its inhibitory effect early in the viral replicative cycle, possibly inhibiting the uncoating of the virus. Genetic studies suggest that a virus protein specified by the virion M2 gene plays an important role in the susceptibility of influenza A virus to inhibition by rimantadine.

MICROBIOLOGY: Rimantadine is inhibitory to the in vitro replication of influenza A virus isolates from each of the three antigenic subtypes, i.e., H1N1, H2N2 and H3N2, that have been isolated from man. Rimantadine has little or no activity against influenza B virus (Ref. 1,2). Rimantadine does not appear to interfere with the immunogenicity of inactivated influenza A vaccine.

A quantitative relationship between the in vitro susceptibility of influenza A virus to rimantadine and clinical response to therapy has not been established.

Susceptibility test results, expressed as the concentration of the drug required to inhibit virus replication by 50% or more in a cell culture system, vary greatly (from 4 ng/mL to 20 µg/mL) depending upon the assay protocol used, size of the virus inoculum, isolates of the influenza A virus strains tested, and the cell types used (Ref. 2).

Rimantadine-resistant strains of influenza A virus have emerged among freshly isolated epidemic strains in closed settings where rimantadine has been used. Resistant viruses have been shown to be transmissible and to cause typical influenza illness. (Ref. 3)

PHARMACOKINETICS: Although the pharmacokinetic profile of Flumadine has been described, no pharmacodynamic data establishing a correlation between plasma concentration and its antiviral effect are available.

The tablet and syrup formulations of Flumadine are equally absorbed after oral administration. The mean ± SD peak plasma concentration after a single 100 mg dose of Flumadine was 74 ± 22 ng/mL (range: 45 to 138 ng/mL). The time to peak concentration was 6 ± 1 hours in healthy adults (age 20 to 44 years). The single dose elimination half-life in this population was 25.4 ± 6.3 hours (range: 13 to 65 hours). The single dose elimination half-life in a group of healthy 71 to 79 year-old subjects was 32 ± 16 hours (range: 20 to 65 hours).

After the administration of rimantadine 100 mg twice daily to healthy volunteers (age 18 to 70 years) for 10 days, area under the curve (AUC) values were approximately 30% greater than predicted from a single dose. Plasma trough levels at steady state ranged between 118 and 468 ng/mL. In these patients no age-related differences in pharmacokinetics were detected. However, in a comparison of three groups of healthy older subjects (age 50-60, 61-70 and 71-79 years), the 71 to 79 year-old group had average AUC values, peak concentrations and elimination half-life values at steady state that were 20 to 30% higher than the other two groups. Steady-state concentrations in elderly nursing home patients (age 68 to 102 years) were 2- to 4-fold higher than those seen in healthy young and elderly adults.

The pharmacokinetic profile of rimantadine in children has not been established. In a group (n=10) of children 4 to 8 years old who were given a single dose (6.6 mg/kg) of Flumadine syrup, plasma concentrations of rimantadine ranged from 446 to 988 ng/mL at 5 to 6 hours and from 170 to 424 ng/mL at 24 hours. In some children drug was detected in plasma 72 hours after the last dose.

Following oral administration, rimantadine is extensively metabolized in the liver with less than 25% of the dose excreted in the urine as unchanged drug. Three hydroxylated metabolites have been found in plasma. These metabolites, an additional conjugated metabolite and parent drug account for 74 ± 10% (n=4) of a single 200 mg dose of rimantadine excreted in urine over 72 hours.

In a group (n=14) of patients with chronic liver disease, the majority of whom were stabilized cirrhotics, the pharmacokinetics of rimantadine were not appreciably altered following a single 200 mg oral dose compared to 6 healthy subjects who were sex, age and weight matched to 6 of the patients with liver disease. After administration of a single 200 mg dose to patients (n=10) with severe hepatic dysfunction, AUC was approximately 3-fold larger, elimination half-life was approximately 2-fold longer and apparent clearance was about 50% lower when compared to historic data from healthy subjects.

Studies of the effects of renal insufficiency on the pharmacokinetics of rimantadine have given inconsistent results. Following administration of a single 200 mg oral dose of rimantadine to 8 patients with a creatinine clearance (CLcr) of 31-50 mL/min and 6 patients with a CLcr of 11-30 mL/min, the apparent clearance was 37% and 16% lower, respectively, and plasma metabolite concentrations were higher when compared to weight-, age-, and sex-

matched healthy subjects (n=9, CLcr > 50 mL/min). After a single 200 mg oral dose of rimantadine was given to 8 hemodialysis patients (CLcr 0-10 mL/min), there was a 1.6-fold increase in the elimination half-life and a 40% decrease in apparent clearance compared to age-matched healthy subjects. Hemodialysis did not contribute to the clearance of rimantadine.

The in vitro human plasma protein binding of rimantadine is about 40% over typical plasma concentrations. Albumin is the major binding protein.

INDICATIONS AND USAGE: Flumadine is indicated for the prophylaxis and treatment of illness caused by various strains of influenza A virus in adults.

Flumadine is indicated for prophylaxis against influenza A virus in children.

PROPHYLAXIS: In controlled studies of children over the age of 1 year, healthy adults and elderly patients, Flumadine has been shown to be safe and effective in preventing signs and symptoms of infection caused by various strains of influenza A virus. Early vaccination on an annual basis as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee is the method of choice in the prophylaxis of influenza unless vaccination is contraindicated, not available or not feasible. Since Flumadine does not completely prevent the host immune response to influenza A infection, individuals who take this drug may still develop immune responses to natural disease or vaccination and may be protected when later exposed to antigenically-related viruses. Following vaccination during an influenza outbreak, Flumadine prophylaxis should be considered for the 2 to 4 week time period required to develop an antibody response. However, the safety and effectiveness of Flumadine prophylaxis have not been demonstrated for longer than 6 weeks.

TREATMENT: Flumadine therapy should be considered for adults who develop an influenza-like illness during known or suspected influenza A infection in the community. When administered within 48 hours after onset of signs and symptoms of infection caused by influenza A virus strains, Flumadine has been shown to reduce the duration of fever and systemic symptoms.

CONTRAINDICATIONS: Flumadine is contraindicated in patients with known hypersensitivity to drugs of the adamantane class, including rimantadine and amantadine.

PRECAUTIONS: *GENERAL:* An increased incidence of seizures has been reported in patients with a history of epilepsy who received the related drug amantadine. In clinical trials of Flumadine, the occurrence of seizure-like activity was observed in a small number of patients with a history of seizures who were not receiving anticonvulsant medication while taking Flumadine. If seizures develop, Flumadine should be discontinued.
The safety and pharmacokinetics of rimantadine in renal and hepatic insufficiency have only been evaluated after single dose administration. In a single dose study of patients with anuric renal failure, the apparent clearance of rimantadine was approximately 40% lower and the elimination half-life was 1.6-fold greater than that in healthy age-matched controls. In a study of 14 persons with chronic liver disease (mostly stabilized cirrhotics), no alterations in the pharmacokinetics were observed after the administration of a single dose of rimantadine. However, the apparent clearance of rimantadine following a single dose to 10 patients with severe liver dysfunction was 50% lower than reported for healthy subjects. Because of the

potential for accumulation of rimantadine and its metabolites in plasma, caution should be exercised when patients with renal or hepatic insufficiency are treated with rimantadine.

Transmission of rimantadine resistant virus should be considered when treating patients whose contacts are at high risk for influenza A illness. Influenza A virus strains resistant to rimantadine can emerge during treatment and such resistant strains have been shown to be transmissible and to cause typical influenza illness (Ref. 3). Although the frequency, rapidity, and clinical significance of the emergence of drug-resistant virus are not yet established, several small studies have demonstrated that 10% to 30% of patients with initially sensitive virus, upon treatment with rimantadine, shed rimantadine resistant virus. (Ref. 3, 4, 5, 6)

Clinical response to rimantadine, although slower in those patients who subsequently shed resistant virus, was not significantly different from those who did not shed resistant virus. (Ref. 3) No data are available in humans that address the activity or effectiveness of rimantadine therapy in subjects infected with resistant virus.

DRUG INTERACTIONS: Cimetidine: The effects of chronic cimetidine use on the metabolism of rimantadine are not known. When a single 100 mg dose of Flumadine was administered one hour after the initiation of cimetidine (300 mg four times a day), the apparent total rimantadine clearance of this single dose in normal healthy adults was reduced by 18% (compared to the apparent total rimantadine clearance in the same subjects in the absence of cimetidine).

Acetaminophen: Flumadine, 100 mg, was given twice daily for 13 days to 12 healthy volunteers. On day 11, acetaminophen (650 mg four times daily) was started and continued for 8 days. The pharmacokinetics of rimantadine were assessed on days 11 and 13. Coadministration with acetaminophen reduced the peak concentration and AUC values for rimantadine by approximately 11%.

Aspirin: Flumadine, 100 mg, was given twice daily for 13 days to 12 healthy volunteers. On day 11, aspirin (650 mg, four times daily) was started and continued for 8 days. The pharmacokinetics of rimantadine were assessed on days 11 and 13. Peak plasma concentrations and AUC of rimantadine were reduced approximately 10% in the presence of aspirin.

Influenza Virus Vaccine Live, Intranasal (FluMist®): The concurrent use of Flumadine with Influenza Virus Vaccine Live, Intranasal (FluMist®) has not been evaluated. However, because of potential interference between Flumadine and Flumist®, it is advisable that Flumist® not be administered until 48 hours after cessation of Flumadine and that Flumadine not be administered until two weeks after the administration of Flumist® unless medically indicated. The concern about potential interference arises principally from the potential for antiviral drugs to inhibit replication of live vaccine virus.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY: Carcinogenesis: Carcinogenicity studies in animals have not been performed.
Mutagenesis: No mutagenic effects were seen when rimantadine was evaluated in several standard assays for mutagenicity.

Impairment of Fertility: A reproduction study in male and female rats did not show detectable impairment of fertility at dosages up to 60 mg/kg/day (3 times the maximum human dose based on body surface area comparisons).

PREGNANCY: Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Rimantadine is reported to cross the placenta in mice. Rimantadine has been shown to be embryotoxic in rats when given at a dose of 200 mg/kg/day (11 times the recommended human dose based on body surface area comparisons). At this dose the embryotoxic effect consisted of increased fetal resorption in rats; this dose also produced a variety of maternal effects including ataxia, tremors, convulsions and significantly reduced weight gain. No embryotoxicity was observed when rabbits were given doses up to 50 mg/kg/day (5 times the recommended human dose based on body surface area comparisons). However, there was evidence of a developmental abnormality in the form of a change in the ratio of fetuses with 12 or 13 ribs. This ratio is normally about 50:50 in a litter but was 80:20 after rimantadine treatment.

Nonteratogenic Effects: Rimantadine was administered to pregnant rats in a peri- and postnatal reproduction toxicity study at doses of 30, 60 and 120 mg/kg/day (1.7, 3.4 and 6.8 times the recommended human dose based on body surface area comparisons). Maternal toxicity during gestation was noted at the two higher doses of rimantadine, and at the highest dose, 120 mg/kg/day, there was an increase in pup mortality during the first 2 to 4 days postpartum. Decreased fertility of the F1 generation was also noted for the two higher doses. For these reasons, Flumadine should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

NURSING MOTHERS: Flumadine should not be administered to nursing mothers because of the adverse effects noted in offspring of rats treated with rimantadine during the nursing period. Rimantadine is concentrated in rat milk in a dose-related manner: 2 to 3 hours following administration of rimantadine, rat breast milk levels were approximately twice those observed in the serum.

PEDIATRIC USE: In children, Flumadine is recommended for the prophylaxis of influenza A. The safety and effectiveness of Flumadine in the treatment of symptomatic influenza infection in children have not been established. Prophylaxis studies with Flumadine have not been performed in children below the age of 1 year.

ADVERSE REACTIONS: In 1,027 patients treated with Flumadine in controlled clinical trials at the recommended dose of 200 mg daily, the most frequently reported adverse events involved the gastrointestinal and nervous systems.
Incidence >1%: Adverse events reported most frequently (1-3%) at the recommended dose in controlled clinical trials are shown in the table below.

	Rimantadine (n=1027)	Control (n=986)
Nervous System		
Insomnia	2.1%	0.9%
Dizziness	1.9%	1.1%
Headache	1.4%	1.3%
Nervousness	1.3%	0.6%
Fatigue	1.0%	0.9%

Gastrointestinal System						
Nausea		2.8%		1.6%		
Vomiting	1.7%		0.6%			
Anorexia	1.6%		0.8%			
Dry mouth	1.5%		0.6%			
Abdominal Pain		1.4%		0.8%		
Body as a Whole						
Asthenia	1.4%		0.5%			

Less frequent adverse events (0.3 to 1%) at the recommended dose in controlled clinical trials were: *Gastrointestinal System:* diarrhea, dyspepsia; *Nervous System:* impairment of concentration, ataxia, somnolence, agitation, depression; *Skin and Appendages:* rash; *Hearing and Vestibular:* tinnitus; *Respiratory:* dyspnea.

Additional adverse events (less than 0.3%) reported at recommended doses in controlled clinical trials were: Nervous System: gait abnormality, euphoria, hyperkinesia, tremor, hallucination, confusion, convulsions; *Respiratory:* bronchospasm, cough; *Cardiovascular:* pallor, palpitation, hypertension, cerebrovascular disorder, cardiac failure, pedal edema, heart block, tachycardia, syncope; *Reproduction:* non-puerperal lactation; *Special Senses:* taste loss/change, parosmia.
Rates of adverse events, particularly those involving the gastrointestinal and nervous systems, increased significantly in controlled studies using higher than recommended doses of Flumadine. In most cases, symptoms resolved rapidly with discontinuation of treatment. In addition to the adverse events reported above, the following were also reported at higher than recommended doses: increased lacrimation, increased micturition frequency, fever, rigors, agitation, constipation, diaphoresis, dysphagia, stomatitis, hypesthesia and eye pain.

Adverse Reactions in Trials of Rimantadine and Amantadine: In a six-week prophylaxis study of 436 healthy adults comparing rimantadine with amantadine and placebo, the following adverse reactions were reported with an incidence
>1 %.

	Rimantadine 200 mg/day (n=145)		Placebo (n=143)		Amantadine 200 mg/day (n=148)	
Nervous System						
Insomnia	3.4%		0.7%		7.0%	
Nervousness	2.1%		0.7%		2.8%	
Impaired Concentration		2.1%		1.4%		2.1%
Dizziness	0.7%		0.0%		2.1%	
Depression	0.7%		0.7%		3.5%	
Total % of subjects with adverse reactions	6.9%		4.1%		14.7%	
Total % of subjects withdrawn due to adverse reactions	6.9%		3.4%		14.0%	

GERIATRIC USE: Approximately 200 patients over the age of 64 were evaluated for safety in controlled clinical trials with Flumadine® (rimantadine hydrochloride). Geriatric subjects who received either 200 mg or 400 mg of rimantadine daily for 1 to 50 days experienced considerably more central nervous system and gastrointestinal adverse events than

comparable geriatric subjects receiving placebo. Central nervous system events including dizziness, headache, anxiety, asthenia, and fatigue, occurred up to two times more often in subjects treated with rimantadine than in those treated with placebo. Gastrointestinal symptoms, particularly nausea, vomiting, and abdominal pain occurred at least twice as frequently in subjects receiving rimantadine than in those receiving placebo. The gastrointestinal symptoms appeared to be dose related. In patients over 64, the recommended dose is 100 mg, daily (see **Clinical Pharmacology** and **Dosage and Administration**).

OVERDOSAGE: As with any overdose, supportive therapy should be administered as indicated. Overdoses of a related drug, amantadine, have been reported with adverse reactions consisting of agitation, hallucinations, cardiac arrhythmia and death. The administration of intravenous physostigmine (a cholinergic agent) at doses of 1 to 2 mg in adults (Ref. 7) and 0.5 mg in children (Ref. 8) repeated as needed as long as the dose did not exceed 2 mg/hour has been reported anecdotally to be beneficial in patients with central nervous system effects from overdoses of amantadine.

DOSAGE AND ADMINISTRATION: *FOR PROPHYLAXIS IN ADULTS AND CHILDREN:* Adults: The recommended adult dose of Flumadine is 100 mg twice a day. In patients with severe hepatic dysfunction, renal failure (CrCl 10 mL/min.) and elderly nursing home patients, a dose reduction to 100 mg daily is recommended. There are currently no data available regarding the safety of rimantadine during multiple dosing in subjects with renal or hepatic impairment. Because of the potential for accumulation of rimantadine metabolites during multiple dosing, patients with any degree of renal insufficiency should be monitored for adverse effects, with dosage adjustments being made as necessary.

Children: In children less than 10 years of age, Flumadine should be administered once a day, at a dose of 5 mg/kg but not exceeding 150 mg. For children 10 years of age or older, use the adult dose.

FOR TREATMENT IN ADULTS: The recommended adult dose of Flumadine is 100 mg twice a day. In patients with severe hepatic dysfunction, renal failure (CrCl 10 mL/min) and elderly nursing home patients, a dose reduction to 100 mg daily is recommended. There are currently no data available regarding the safety of rimantadine during multiple dosing in subjects with renal or hepatic impairment. Because of the potential for accumulation of rimantadine metabolites during multiple dosing, patients with any degree of renal insufficiency should be monitored for adverse effects, with dosage adjustments being made as necessary. Flumadine therapy should be initiated as soon as possible, preferably within 48 hours after onset of signs and symptoms of influenza A infection. Therapy should be continued for approximately seven days from the initial onset of symptoms.

HOW SUPPLIED: Flumadine® tablets (rimantadine hydrochloride tablets) are supplied as 100 mg tablets (orange, oval-shaped, film-coated) in bottles of 100 (NDC 0456-0521-01). Imprint on tablets: (Front) FLUMADINE 100; (Back) FOREST.

Flumadine® syrup (rimantadine hydrochloride syrup) containing 50 mg of rimantadine hydrochloride per teaspoonful (5 mL) (clear, colorless, raspberry-flavored) is supplied in bottles of 8 oz (NDC 0456-0527-08).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

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