LEFLUNOMIDE (Systemic)

Introduction

VA CLASSIFICATION (Primary)¾MS109

Commonly used brand name(s):Arava.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Antirheumatic (disease-modifying).

Indications

General considerations

For women of childbearing potential and men wishing to father a child, see the Pregnancy/Reproduction section of Precautions to Consider for restrictions on the use of leflunomide 1.

Accepted

Arthritis, rheumatoid (treatment)¾Leflunomide is indicated to alleviate the signs and symptoms of rheumatoid arthritis and to slow joint impairment 1.

Pharmacology/Pharmacokinetics

Note: The active metabolite, A77 1726 (M1), of leflunomide is responsible for all of its pharmacological activity in vivo1.

Therefore, results of the pharmacokinetic studies were based on the activity of M1 1.

Physicochemical characteristics:

Molecular weight¾270.2 1

Mechanism of action/Effect:

Leflunomide, an immunomodulatory agent, inhibits dihydrooratate dehydrogenase 1.

Anti-inflammatory effects have been demonstrated in in vivo and in vitro experimental models 1.

In addition, leflunomide has antiproliferative activity 1.

Absorption:

M1 metabolite is 80% bioavailable 1.

Administration of leflunomide with a high-fat meal has no effect on the plasma concentration of M1 1.

Protein binding:

M1¾Very high (> 99%) 1.

In patients with chronic renal failure, the free fraction of M1 is increased twofold 1.

However, the free fraction of M1 in rheumatoid arthritis patients is only slightly higher than in healthy volunteers 1.

Biotransformation:

Leflunomide is metabolized to M1 and other minor active metabolites 1.

An active metabolite, 4-trifluoromethylaniline, is present in plasma at low concentrations 1.

Although the specific site of leflunomide metabolism is unknown, it has been suggested that the gastrointestinal wall and liver play a role in the metabolism 1.

Half-life:

M1¾2 weeks 1.

Time to peak concentration:

M1¾approximately 6 to 12 hours 1.

Elimination:

Renal, approximately 43% of a radiolabeled leflunomide dose is excreted in the urine, primarily as leflunomide glucuronides and an oxalic acid derivative of M1 1.

Fecal, approximately 48% of a radiolabeled leflunomide dose is eliminated in the feces, primarily as M1 1.

In dialysis¾
Studies have found that M1 is not removable by hemodialysis 1.

Precautions to Consider

Carcinogenicity

No carcinogenic effects of leflunomide were observed in a 2-year bioassay study in rats receiving oral doses of leflunomide of up to 6 mg per kg of body weight (mg/kg) per day (reflects an area under the plasma concentration-time curve [AUC] exposure of 1/40 of the maximum human M1 exposure) 1.

Mutagenicity

Leflunomide demonstrated no mutagenic activity in the Ames test, unscheduled DNA synthesis assay, or in the HGPRT gene mutation assay 1.

However, a minor metabolite of leflunomide, 4-trifluoromethylaniline (TFMA), was demonstrated to be mutagenic in the Ames test and HGPRT gene mutation assay 1.

There was no evidence of clastogenic activity with leflunomide or TFMA in the in vivo mouse micronucleus assay or in the cytogenic test in Chinese hamster bone marrow cells 1.

However, there was evidence of clastogenic activity with TFMA in the in vitro assay for chromosome aberration in the Chinese hamster cells 1.

Pregnancy/Reproduction

Fertility¾Fertility studies in adult males have not been done to evaluate the increased risk of male-mediated fetal toxicity 1.

However, it is recommended that men intending to father a child minimize risks by discontinuing use of leflunomide and starting treatment with cholestyramine 8 grams three times a day for 11 days according to the manufacturer's recommended drug elimination procedure for leflunomide 1.

No impairment of fertility was demonstrated in reproduction studies in male and female rats receiving doses of leflunomide of up to 4 mg/kg (reflects an AUC exposure of 1/30 of the maximum human M1 exposure) 1.

Pregnancy¾Use of leflunomide is contraindicated during pregnancy because of its potential to cause fetal harm 1.

Patients of childbearing potential may use leflunomide only if reliable contraception is being used and pregnancy has been excluded prior to starting leflunomide treatment. Pregnancy should be avoided during treatment with leflunomide and prior to the completion of the drug elimination procedure after receiving leflunomide 1.

The drug elimination procedure should be used immediately if the patient becomes pregnant while taking leflunomide 1.

If leflunomide is used by a pregnant woman, or if a woman becomes pregnant during treatment, she should be advised that this medication may harm the fetus 1.

A study in rats during the organogenesis period showed that leflunomide doses of up to 15 mg/kg per day (reflects AUC exposure of 1/10 of the maximum human exposure) were teratogenic, resulting in anomalies such as anophthalmia or microopthalmia and internal hydrocephalus 1.

In addition, leflunomide caused a decrease in maternal body weight and an increase in embryolethality with a decrease in the body weight of surviving fetuses 1.

A study in rabbits during the organogenesis period showed that leflunomide doses of up to 10 mg/kg per day (reflects an AUC exposure equivalent to the maximum human exposure) resulted in fused, dysplastic sternebrae. However, there were no teratogenic effects observed in rats or rabbits receiving leflunomide doses of 1 mg/kg 1.

In female rats receiving leflunomide at doses of 1.25 mg beginning 14 days before mating and continuing until the end of lactation, a 90% decrease in the postnatal survival of the offspring was observed 1.

FDA Pregnancy Category X 1.

Breast-feeding

It is not known whether leflunomide is distributed into the breast milk of humans and problems have not been documented. However, use is not recommended for nursing mothers 1.

Pediatrics

No information is available on whether the risk of leflunomide-induced adverse effects is increased in children up to 18 years of age 1.

However, because of this medication's potential toxicity, use is not recommended in pediatric patients 1.

Geriatrics

No information is available on the relationship of age to the effects of leflunomide in geriatric patients 1.

However, a dosage adjustment is not recommended in patients older than 65 years of age 1.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Charcoal, activated or

Cholestyramine

(concurrent use of these medications will significantly decrease the plasma concentration of M1 by inhibiting gastrointestinal absorption 1)

>> Hepatotoxic medications (see Appendix II), such as:
Methotrexate

(concurrent use with these medications may increase the risk of side effects and medication-induced hepatic toxicity; in a small study evaluating the concurrent use of leflunomide (100 mg per day followed by 10 to 20 mg per day) and methotrexate (10 to 25 mg per week with folate), an increased risk of hepatotoxicity was reported; dosage adjustment may be needed 1)

Rifampin

(concurrent use with rifampin may increase the plasma concentration of leflunomide; caution is recommended 1)

>> Vaccines, live virus

(leflunomide may cause immunosuppression; use is not recommended 1)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]), serum or

Alkaline phosphatase, serum or

Aspartate aminotransferase (AST [SGOT]), serum or

(values may be increased 1)

Bilirubin, serum

(concentrations may be increased)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

>> Bone marrow dysplasia

>> Immunodeficiency, severe

>> Infections, severe or uncontrolled

(leflunomide may cause immunosuppression; use is not recommended 1)

>> Hepatic disease

>> Hepatic function impairment, severe

>> Hepatitis B or C, positive serology

(may increase the risk of hepatotoxicity; use is not recommended 1)

Risk-benefit should be considered when the following medical problems exist

>> Renal function impairment

(studies in patients with chronic renal impairment have reported a twofold increase in the plasma concentration of leflunomide; caution is recommended 1)

Sensitivity to leflunomide 1

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Hepatic function tests

(values should be monitored at baseline and then monthly thereafter; monitoring may be continued according to individual patient's response after levels are stable 1)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent

Bronchitis 1 congestion in chest); cough); difficult or painful breathing); hepatotoxicity 1 loss of appetite); nausea and/or vomiting); yellow eyes or skin); hypertension 1 dizziness); headache, severe or continuing); respiratory infection 1 cough); (fever); sneezing); sore throat); urinary tract infection 1 bloody or cloudy urine); difficult, burning, or painful urination); frequent urge to urinate)

Incidence less frequent

Anemia 1 unusual tiredness or weakness); chest pain 1; dyspnea 1 shortness of breath); gastritis burning feeling in chest or stomach); indigestion); tenderness in stomach area); gastroenteritis 1 severe abdominal pain); diarrhea); loss of appetite); nausea); weakness); palpitations 1 pounding heartbeat); paresthesias 1 burning, prickling, or tingling sensations in fingers and/or toes); synovitis 1 joint or muscle pain or stiffness); tachycardia 1 fast heartbeat); tenosynovitis 1 joint or muscle pain or stiffness)
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Abdominal pain 1 (stomach pain); alopecia 1 (hair loss); back pain 1; diarrhea 1; dizziness 1; dyspepsia 1 (heartburn); headache 1; nausea and/or vomiting 1; skin rash 1; weight loss, unexplained 1
Incidence less frequent

Acne 1; anorexia 1 (decreased appetite); anxiety 1; conjunctivitis 1 (red or irritated eyes); constipation 1; dry mouth 1; fever 1; flatulence 1 (gas); malaise 1 (unusual tiredness or weakness); mouth ulcer 1 (irritation or soreness of mouth); pharyngitis (pain or burning in throat); pruritus 1 (itching of the skin); rhinitis 1 (runny nose); sinusitis 1 (headache; runny nose)

Overdose

For specific information on the agents used in the management of leflunomide overdose, see:
· Charcoal, Activated (Oral-Local) monograph; or
· Cholestyramine (Oral-Local)monograph.
For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Treatment of overdose

To enhance elimination¾
Administration of activated charcoal orally or via nasal gastric tube 50 grams every 6 hours for 24 hours post-ingestion 1.

Administration of cholestyramine 8 grams three times a day for 24 hours post-ingestion
Supportive care¾General supportive measures should be instituted 1.

Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Leflunomide (Systemic)¾Introductory Version .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):

Before using this medication

>> Conditions affecting use, especially:

Sensitivity to leflunomide
Pregnancy¾Use of leflunomide is contraindicated during pregnancy because of its potential harm to the fetus; advisability of using contraception; telling physician immediately if pregnancy is suspected
Breast-feeding¾Use of leflunomide is not recommended for nursing mothers
Use in children¾Use of leflunomide is not recommended in children
Other medications, especially hepatotoxic medications or live vaccines
Other medical problems, especially bone marrow dysplasia, immunodeficiency, infection (severe or uncontrolled), hepatic disease, hepatic function impairment (severe), hepatitis B or C, or renal function impairment
Proper use of this medication

>> Importance of not taking more medication than the amount prescribed

>> Proper dosing
Missed dose: Taking as soon as possible; skipping missed dose if almost time for next dose; not doubling doses
>> Proper storage
Precautions while using this medication

>> Regular visits to physician to check progress during therapy

>> Stopping medication immediately and checking with physician if pregnancy is suspected, since leflunomide may cause birth defects in humans

>> Men taking leflunomide should use condoms during sexual intercourse, since leflunomide may cause birth defects in the children of men taking this medication at the time of conception; men intending to father a child should discontinue leflunomide and contact their physician immediately

>> Avoiding alcoholic beverages, which may increase the risk of hepatotoxicity

>> Avoiding immunizations unless approved by physician

Side/adverse effects

Signs of potential side effects, especially bronchitis, hepatotoxicity, hypertension, respiratory infection, urinary tract infection, anemia, chest pain, dyspnea, gastritis, gastroenteritis, palpitations, paresthesias, synovitis, tachycardia, or tenosynovitis

General Dosing Information

As a result of the long half-life of leflunomide, caution should be used in administering live vaccines after stopping leflunomide treatment 1.

After completing leflunomide treatment, the following elimination procedure is recommended by the manufacturer to obtain nondetectable plasma levels of leflunomide (0.02 mg/L):
· Administer cholestyramine 8 grams three times a day for 11 days 1.

The 11 days do not have to be consecutive 1.

However, to lower the plasma level rapidly, cholestyramine should be administered for 11 days consecutively 1.

· Use two different tests at least 14 days apart to confirm that plasma levels are less than 0.02 mg/L 1.

If plasma levels are higher than 0.02 mg/L, additional cholestyramine treatment should be considered 1.

Note: If the elimination procedure is not used, it may take up to 2 years before plasma levels of M1 are less than 0.02 mg/L due to individual variation in drug clearance 1.

If a patient develops increased liver enzyme levels, the following guidelines are recommended for dosage adjustment or discontinuation based on the severity and persistence of the elevations:
· For elevations of alanine transferase (ALT [SGPT]) greater than two times the upper normal limit, the dose of leflunomide should be reduced to 10 mg a day 1.

· For elevations of ALT between two and three times the upper normal limit that persist despite the dose reduction, a liver biopsy is recommended if it is desirable to continue treatment with leflunomide 1.

· For elevations that are greater than three times the upper normal limit that continue with a dosage reduction and the administration of cholestyramine, leflunomide should be discontinued; then cholestyramine should be readministered with close monitoring and additional doses of cholestyramine as needed 1.

Oral Dosage Forms

LEFLUNOMIDE TABLETS

Usual adult dose

Arthritis, rheumatoid¾
Oral, initially 100 mg once a day for three days, followed by a maintenance dose of 20 mg a day 1.

Note: Maintenance dose may be decreased to 10 mg a day according to patient response 1.

Usual adult prescribing limits

20 mg in twenty-four hours 1.

Usual pediatric dose

Safety and efficacy have not been established in children up to 18 years of age 1.

Usual geriatric dose

See Usual adult dose 1.

Strength(s) usually available

U.S.¾10 mg (Rx)[Arava 1 (colloidal silicon dioxide) (crospovidone) (hydroxypropyl methylcellulose) (lactose monohydrate) (magnesium stearate) (polyethylene glycol) (povidone) (starch) (talc) (titanium dioxide)]

20 mg (Rx)[Arava 1 (colloidal silicon dioxide) (crospovidone) (hydroxypropyl methylcellulose) (lactose monohydrate) (magnesium stearate) (polyethylene glycol) (povidone) (starch) (talc) (titanium dioxide) (yellow ferric oxide)]

100 mg (Rx)[Arava 1 (colloidal silicon dioxide) (crospovidone) (hydroxypropyl methylcellulose) (lactose monohydrate) (magnesium stearate) (polyethylene glycol) (povidone) (starch) (talc) (titanium dioxide)]

Packaging and storage:

Store at 25 °C (77 °F). Protect from light