Leflunomide (Arava®)

Leflunomide (Arava) is an isoxazole immunomodulatory agent that inhibits dihydroorotate dehydrogenase (a mitochondrial enzyme involved in de novo pyrimidine synthesis) and has antiproliferative activity and anti-inflammatory effects.

Resources from Manufacturer

Full Prescribing Information

Indications and Dosing in Rheumatology

Leflunomide is indicated for:

- Adults with active rheumatoid arthritis

Dosing:

- Optional loading dosing: 100 mg orally daily for 3 days
  - For patients at low risk for leflunomide-associated hepatotoxicity or myelosuppression
- Maintenance dosing: 20 mg orally daily
  - Maximum recommended daily dosage is 20 mg once daily. If 20 mg is not tolerated, may decrease dosage to 10 mg once daily.

Contraindications

- Pregnancy
- Severe hepatic impairment
- Known hypersensitivity
- Current teriflunomide treatment

Warnings and Precautions

- Embryo-fetal toxicity–Leflunomide may cause fetal harm when administered to pregnant women, including teratogenicity and embryo-lethality. Exclude pregnancy prior to initiating leflunomide therapy and advise use of effective contraceptives in females of reproductive potential. Stop leflunomide and use accelerated drug elimination procedure if the patient becomes pregnant.
- Hepatotoxicity–Severe liver injection and fatal liver failure have been reported. Avoid use in patients with pre-existing liver disease or those with ALT > 2x ULN before treatment. Monitor LFTs monthly after start then every 6-8 weeks during treatment, with interruption in therapy recommended if ALT > 3x ULN.
- Serious Infections–Do not start leflunomide in patients with a severe active infection, immunodeficiency, or bone marrow dysplasia. Pancytopenia, agranulocytosis, thrombocytopenia, and opportunistic infections have been reported, however most frequently in patients on concomitant methotrexate, immunosuppressive agents, or history of hematologic abnormalities.
- Stevens-Johnson syndrome–SJS, toxic epidermal necrolysis, and drug reactions with eosinophilia and systemic symptoms (DRESS) have been reported. If occurs, discontinue leflunomide and use accelerated drug elimination procedure.
- Peripheral neuropathy–If patient develops symptoms consistent with peripheral neuropathy, evaluate further and consider discontinuing leflunomide.

Warnings and Precautions *continued*

- Interstitial lung disease–May be fatal. New onset or worsening symptoms may necessitate discontinuation of leflunomide and consider accelerated drug elimination procedure.
- Increase blood pressure–Monitor and treat.

Adverse Reactions

Common (≥ 10%):

- Diarrhea
- Respiratory infection
- Nausea, dyspepsia
- Headache
- Rash
- Abnormal liver enzymes

Medication Strength and Preparations

- 10 mg and 20 mg tablets

Medication Administration and Monitoring

- Take 1 tablet by mouth once daily.
- Food does not have a significant impact on absorption or serum concentration.
- Store at room temperature and protect from light.

Accelerated drug elimination procedure:

- After leflunomide discontinuation, the active metabolite (teriflunomide) is slowly eliminated from the plasma and may take up to 2 years to reach undetectable plasma concentrations. Accelerated drug elimination procedure should be considered for rapid reduction of drug levels in patients who have experienced a severe adverse reaction, has become pregnant, or of childbearing potential.
- Elimination procedure:
  - ❑ Administer cholestyramine 8 grams orally 3 times daily for 11 days.
  - ❑ Alternatively, administer 50 grams of activated charcoal powder (made into suspension) orally every 12 hours for 11 days.
  - ❑ Verify plasma teriflunomide concentrations <0.02 mg/L by 2 separate tests at least 14 days apart. Repeat procedure if concentrations are >0.02 mg/L.
- The duration of accelerated drug elimination treatment may be modified based on the clinical status and tolerability of the elimination procedure.

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ACR/ARP Medication Guide

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The Interprofessional Division of the American College of Rheumatology