**Leflunomide (le-flu-nom-ide)**

**Synonyms:**

- Arava

**Classification:**

- Therapeutic: antirheumatics (DMARDs)
- Pharmacologic: immune response modifiers, pyrimidine synthesis inhibitors

**Pregnancy Category X**

**Indications:**

- Rheumatoid arthritis (disease-modifying agent).

**Action:**

- Inhibits an enzyme required for pyrimidine synthesis; has antiproliferative and anti-inflammatory effects.

**Therapeutic Effects:**

- Decreased pain and inflammation, slowed structural progression and improved physical function.

**Pharmacokinetics:**

- **Absorption:** Tablets are 80% absorbed following oral administration; rapidly converted to the M1 metabolite, which is responsible for pharmacologic activity.
- **Distribution:** Crosses the placenta.
- **Protein Binding:** 99%.
- **Metabolism and Excretion:** Extensively metabolized with metabolites excreted in urine (43%) and feces (48%). Also undergoes biliary recycling.
- **Half-life:** 14–18 days.

**TIME/ACTION PROFILE (antirheumatic effect)**

<table>
<thead>
<tr>
<th>ROUTE</th>
<th>ONSET</th>
<th>PEAK</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO</td>
<td>1 mo</td>
<td>3–6 mo</td>
<td>wk–mos†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Due to persistence of active metabolite

**Contraindications/Precautions:**

- **Contraindicated in:**
  - Hypersensitivity; Compromised immune function, including bone marrow dysplasia or severe uncontrolled infection; Concurrent vaccination with live vaccines; Hepatic impairment; OB: May cause fetal abnormalities or death. Contact Pregnancy Registry if accidental exposure occurs; Lactation: Lactation.
  - Men: Should not be used in men attempting to father a child.

- **Use Cautiously in:**
  - Renal insufficiency; History of interstitial lung disease; Patients >60 yr, with diabetes, or taking neurotoxic medications (increased risk of peripheral neuropathy); OB: Women with childbearing potential must use two forms of birth control. Should not be used in men attempting to father a child.

**Adverse Reactions/Side Effects:**

- **CNS:** Headache, dizziness, weakness.
- **Resp:** Interstitial lung disease, bronchitis, cough, sinusitis.
- **GI:** Diarrhea, nausea, abdominal pain, anorexia, dyspepsia, gastroenteritis, liver enzymes, mouth ulcers, vomiting.
- **GU:** Urinary tract infection.
- **Derm:** Stevens-Johnson syndrome, toxic epidermal necrolysis, alopecia, rash, dry skin, eczema, pruritus.
- **F and E:** Hypokalemia.
- **Metab:** Weight loss.
- **MS:** Arthritis, back pain, joint disorder, leg cramps, sensorimotor neuropathy.
- **Neuro:** Paresthesia, peripheral neuropathy, myelitis, allergic reactions, fever, disseminated infections including sepsis and tuberculosis reactivation, pain.

**Drug Interactions:**

- **Drug-Drug:** Cholestyramine and activated charcoal cause a rapid and significant fall in blood levels of active metabolite. Concurrent use of methotrexate and other hepatotoxic drugs increases risk of hepatotoxicity. Concurrent administration of rifampin increases blood levels of the active metabolite. May increase risk of bleeding with warfarin.

**Route/Dosage**

- **PO (Adults):** Loading dose—100 mg daily for 3 days; maintenance dosing—20 mg/day (if intolerance occurs, dose may be reduced to 10 mg/day).

**NURSING IMPLICATIONS**

- **Assess range of motion and degree of swelling and pain in affected joints before and periodically during therapy.
- **Monitor for signs and symptoms of interstitial lung disease (new onset or worsening cough or dyspnea, associated with fever). May require discontinuation of therapy; consider drug elimination procedure if needed.
- **Assess for rash periodically during therapy. May cause Stevens-Johnson syndrome or toxic epidermal necrolysis. Discontinue therapy if severe rash occurs; discontinue if recurrence occurs, dose may be reduced to 10 mg/day.**
or if accompanied with fever, general malaise, fatigue, muscle or joint aches, histoid, oral lesions, hepatomegaly and/or eosino-philia.

- **Lab Test Considerations:** Monitor liver function throughout therapy. Assess ALT at baseline, then monthly during initial 6 mo of therapy, then every 6–8 wk. If given concurrently with methotrexate, monitor ALT, AST, and serum albumin monthly. May cause an increase in serum creatinine, which is usually reversible with reduction in dose or discontinuation, but may be fatal. If ALT is 2–3 times the upper limit of normal, reduce dose to 10 mg/day and continue therapy. Monitor closely after dose reduction; plasma levels may not return to normal for several weeks due to long half-life. If ALT is 2–3 times the upper limit of normal persist after dose reduction or ALT >5 times the upper limit of normal occur, discontinue leflunomide and administer cholestyramine (see Toxicity and Overdose). Monitor closely and maintain plasma cholestyramine concentration as indicated.

- **Monitor CBC with platelets monthly for 6 mo following initiation of therapy and every 6–8 wk thereafter. If used with methotrexate or other immunosuppressive therapy continue monitoring monthly. If bone marrow depression occurs, discontinue leflunomide and begin decreasing levels with cholestyramine (see Implementation).

- **May rarely cause an increase of alkaline phosphatase and bilirubin.**

- **Toxicity and Overdose:** If overdose or significant toxicity occurs, cholestyramine 8 g 3 times daily for 11 days. (Days do not need to be consecutive unless rapid lowering of levels is desired) 0.02 mg/L after stopping treatment with leflunomide. Administer cholestyramine 8 g 3 times daily for 11 days. (Days do not need to be consecutive unless rapid lowering of levels is desired). Verify plasma levels 0.02 mg/L by 2 separate tests at least 14 days apart. If plasma levels >0.02 mg/L, consider additional cholestyramine treatment. Plasma levels may take up to 2 yr to reach undetectable levels without drug elimination procedures.

**Potential Nursing Diagnoses**

- Impaired physical mobility (Indications)
- Acute pain (Indications)

**Implementation**

- Administer a tuberculin skin test prior to administration of leflunomide. Patients with active latent TB should be treated for TB prior to therapy.
- **PO:** Initiate therapy with loading dose of 100 mg/day for 3 days, followed by 20 mg daily dose. May discontinue 10 mg/day if not well tolerated.
- **Drug Elimination Procedure:** Recommended to achieve undetectable plasma levels >0.02 mg/L after stopping treatment with leflunomide. Administer cholestyramine 8 g 3 times daily for 11 days. (Days do not need to be consecutive unless rapid lowering of levels is desired). 0.02 mg/L after stopping treatment with leflunomide. Administer cholestyramine 8 g 3 times daily for 11 days. (Days do not need to be consecutive unless rapid lowering of levels is desired). Verify plasma levels 0.02 mg/L by 2 separate tests at least 14 days apart. If plasma levels >0.02 mg/L, consider additional cholestyramine treatment. Plasma levels may take up to 2 yr to reach undetectable levels without drug elimination procedures.

**Patient/Family Teaching**

- **Initiate therapy with loading dose of 100 mg/day for 3 days, followed by 20 mg dose. May discontinue 10 mg/day if not well tolerated.**
- Discuss with patient the importance of serial routine lab tests to monitor for side effects.
- Instruct patient to consult health care professional if rash, mucous membrane lesions, abnormal findings, abnormal pain, paresthesia, or symptoms of interstitial lung disease occur.
- Discontinue patient prior to vaccinations with live vaccines during and following therapy. If symptoms of childhood vaccine-related leflunomide have serious effects. Women planning to become pregnant must undergo the drug elimination procedure (see Implementation) and verify that the M1 metabolite plasma levels are <0.02 mg/L. Men wishing to father a child should also take cholestyramine 8 g 3 times daily for 11 days to minimize any possible risk.
- Emphasize the importance of routine lab tests to monitor for side effects.

**Evaluation/Desired Outcomes**

- Decrease in signs and symptoms of chronic inflammatory arthropathy and slowing of structural damage as evidenced by x-ray erosions and joint narrowing.
- Improved physical function.

Why was this drug prescribed for your patient?