**DRUG CLASS:** Disease Modifying Anti-Rheumatic Drug (DMARD)

**BRAND (generic) NAME:**
- Arava® (leflunomide) 10 mg oral tablet (GCN = 067031)
- 20 mg oral tablet (GCN = 067032)
- 100 mg oral tablet (GCN = 067033)

Tablets are unscored. The 100 mg tablets are only available in a blister pack for use as a loading dose.

**FDA INDICATIONS:** Arava® is indicated for the treatment of active rheumatoid arthritis (RA) to reduce signs and symptoms, to retard structural damage as evidenced by x-ray erosions and joint space narrowing, and to improve physical function.

**ICD-9 CODE:** Rheumatoid arthritis: 714.0

**RATIONALE:**
- The goal of RA treatment is to alleviate patient symptoms and prevent joint damage. Non-steroidal anti-inflammatory drugs (NSAIDs, including COX-2 inhibitors) alleviate some of the symptoms of the disease but do not modify the course of the disease. Low-dose oral steroids also alleviate symptoms and may have a beneficial effect on outcomes. Disease-modifying anti-rheumatic drugs (DMARDs) are thought to potentially alter the course of the disease by reducing or preventing the occurrence of erosions and joint deformity. It typically takes 3 to 6 months before the benefits of DMARDs are seen. Traditional DMARDs include hydroxychloroquine, sulfasalazine, cyclosporine, azathioprine, D-penicillamine, auranofin, methotrexate, and gold.

**BENEFIT DESIGN:**
Coverage is provided immediately (without generating a coverage review process) in the presence of a prescription within the previous 18 months for any of the following disease-modifying anti-rheumatic drugs (DMARDs):
- Methotrexate
- Etanercept (Enbrel®)
- Anakinra (Kineret™)
- Leflunomide (Arava®)
- Adalimumab (Humira®)

In situations where none of the above DMARDs exist in history, coverage for Arava® is determined through the coverage authorization process below.

**COVERAGE AUTHORIZATION CRITERIA:**
Coverage is provided for the treatment of rheumatoid arthritis in the following situations:
- Patient has experienced a therapeutic failure with methotrexate or has had an inadequate response to methotrexate
- Patient is unable to receive methotrexate (e.g., use of methotrexate is contraindicated in the patient)

**BLACK BOX WARNINGS:**
Pregnancy must be excluded before the start of treatment with Arava®. Arava® is contraindicated in pregnant women, or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during Arava treatment prior to the completion of the drug elimination procedure after Arava treatment.

**RATIONALE:**
A treatment program that includes methotrexate as initial therapy may be considered for most patients unless a patient has a contraindication to or is unable to receive methotrexate (e.g., such as in the presence of liver or lung disease). Arava® may be used in combination or in place of methotrexate in patients who do not respond adequately to methotrexate alone.
PROVIDER EDUCATION:

1. Common adverse effects include headache, diarrhea, abnormal liver enzymes, alopecia, rash, and nausea.

2. A drug elimination procedure involving the use of cholestyramine (8 grams TID for 11 days) is recommended if patients experience serious toxicity, hypersensitivity, and in women of childbearing age who discontinue the drug.


DOSAGE AND ADMINISTRATION:

The recommended leflunomide regimen for RA is 100 mg once daily for 3 days followed by a maintenance dose of 20 mg once daily. Doses greater than 20 mg per day are not recommended because of an increased risk of alopecia, weight loss, and elevations of liver function tests. The dose may be decreased to 10 mg once daily if 20 mg is poorly tolerated.

RISK FACTORS/CONTRAINDICATIONS:

Based on teratogenicity in animal studies, leflunomide is considered Pregnancy Category X. If a woman becomes pregnant while taking leflunomide, a drug elimination procedure with cholestyramine should be instituted as soon as possible. It is unclear whether leflunomide passes into breast milk. Because of the potential for adverse reactions in the nursing infant, the manufacturer recommends against the use of leflunomide in women who are breastfeeding.

Leflunomide is not recommended for patients with severe immunodeficiency, bone marrow dysplasia, or severe uncontrolled infections. Pancytopenia has been reported rarely in patients receiving leflunomide, most of whom were also taking methotrexate or other immunosuppressive agents, or had recently discontinued these drugs. Leflunomide should be used cautiously and with frequent clinical and hematologic monitoring in patients with a prior history of a significant hematologic abnormality.

Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients receiving leflunomide. A drug elimination procedure should be used in patients who develop these conditions.

Leflunomide is associated with elevation in liver enzymes, particularly AST and ALT, in a significant number of patients. Most transaminase elevations are mild (≤ 2-fold the upper limit of normal) and usually resolve while continuing treatment. Marked elevations (> 3-fold the upper limit of normal) occur in up to 4.4% of patients and usually reverse with dose reduction or discontinuation of therapy. The manufacturer recommends that ALT should be performed at baseline and monitored initially at monthly intervals; then, if stable, at intervals determined by an individual's clinical situation. The manufacturer does not recommend the use of leflunomide in patients with severe liver impairment or evidence of hepatitis B or C viruses.

DRUG INTERACTIONS:

- In an open clinical trial, 30 patients received methotrexate and leflunomide concurrently. A pharmacokinetic study in 12 of these patients did not detect a drug interaction between leflunomide and methotrexate. However, the potential for hepatotoxicity may increase with coadministration of these two agents. Liver enzyme levels doubled or tripled in 5 of 30 patients. In 2 of these patients, liver enzyme elevations resolved despite continuation of both agents; in the remaining 3 patients liver enzyme elevations resolved with discontinuation of leflunomide.

- Based on an in vitro study, leflunomide may inhibit hepatic cytochrome P450 2C9. This enzyme is responsible for the metabolism of amitriptyline, diclofenac, ibuprofen, imipramine, phenytoin, tolbutamide, and S-warfarin.

- Multiple doses of rifampin increase peak levels of leflunomide’s active metabolite by about 40%.

- No data are available on the efficacy or safety of vaccination during leflunomide therapy. The use of live vaccines is not recommended. The long half-life (2 weeks) of the active metabolite of leflunomide should be considered if use of a live vaccine is being contemplated after the discontinuation of leflunomide.

REFERENCES:


