WARNING: EMBRYO-FETAL TOXICITY and HEPATOTOXICITY

See full prescribing information for complete boxed warning.

Embryo-Fetal Toxicity

• Teratogenicity and embryo-fatality occurred in animals administered leflunomide. (5.1, 8.1)

• Exclude pregnancy prior to initiating ARAVA therapy. (5.1, 8.3)

• Advise use of effective contraception in females of reproductive potential during treatment and during a drug elimination procedure. (5.1, 5.3, 8.3)

• Stop ARAVA and use an accelerated drug elimination procedure if the patient becomes pregnant. (5.1, 5.3, 8.1)

Hepatotoxicity

• Severe liver injury and fatal liver failure have been reported. (5.2)

• Avoid ARAVA use in patients with pre-existing liver disease, or those with serum alanine aminotransferase (ALT) >2 x ULN. (5.2, 8.6)

• Use caution when ARAVA is given with other potentially hepatotoxic drugs. (5.2)

• Monitor ALT levels. Interrupt ARAVA treatment if ALT elevation >3-fold ULN. If likely leflunomide-induced, start accelerated drug elimination procedure and monitor liver tests weekly until normalized. (5.2, 5.3)

INDICATIONS AND USAGE

ARAVA is a pyrimidine synthesis inhibitor indicated for the treatment of adults with active rheumatoid arthritis. (1)

DOSEAGE AND ADMINISTRATION

• Loading dosage for patients at low risk for ARAVA-associated hepatotoxicity and ARAVA-associated myelosuppression: 100 mg daily for 3 days. (2.1)

• Maintenance dosage: 20 mg daily. (2.1)
  - Maximum recommended daily dosage: 20 mg once daily. (2.1)
  - If 20 mg once daily is not tolerated, may decrease dosage to 10 mg once daily. (2.1)

• Screen patients for active and latent tuberculosis, pregnancy test (females), blood pressure, and laboratory tests before starting ARAVA. (2.2)

DOSEAGE FORMS AND STRENGTHS

Tables: 10 mg, 20 mg, 100 mg. (3)

CONTRAINdicATIONS

• Pregnancy: (4, 5.1, 8.1)

• Severe hepatic impairment: (4, 5.2)

• Hypersensitivity to ARAVA or any of its inactive components: (4)

• Current teriflunomide treatment: (4)

WARNINGS AND PRECAUTIONS

• After stopping ARAVA, it is recommended that an accelerated drug elimination procedure be used to reduce the plasma concentrations of the active metabolite, teriflunomide. (5.3)

• Severe infections (including sepsis), pancytopenia, agranulocytosis, and thrombocytopenia: Stop ARAVA and use accelerated elimination procedure. Do not start ARAVA in patients with active infection. Monitor CBCs during treatment with ARAVA. (5.4)

• Stevens-Johnson syndrome and toxic epidermal necrolysis: Drug reaction with eosinophilia and systemic symptoms (DRESS): Stop ARAVA and use accelerated elimination procedure. (5.5)

• Peripheral neuropathy: If patient develops symptoms consistent with peripheral neuropathy, evaluate patient and consider discontinuing ARAVA. (5.7)

• Intestinal lung disease: May be fatal. New onset or worsening symptoms may necessitate discontinuation of ARAVA and initiation of accelerated elimination procedure. (5.8)

• Increased blood pressure: Monitor and treat. (5.10)

ADVERSE REACTIONS

The most commonly reported adverse reactions (>10%) regardless of relation to ARAVA treatment were diarrhea, respiratory infection, nausea, headache, rash, abnormal liver enzymes, and dyspepsia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

• Drugs metabolized by CYP2C8 and OAT3 transporters: Monitor patients because teriflunomide may increase exposure of these drugs. (7)

• Teriflunomide may increase exposure of ethinyl estradiol and levoestrigenol. Choose an appropriate oral contraceptive. (7)

• Drugs metabolized by CYP1A2: Monitor patients because teriflunomide may decrease exposure of these drugs. (7)

• Warfarin: Monitor INR as teriflunomide may decrease INR. (7)

• Drugs metabolized by BCRP and OATP1B1/B3 transporters: Monitor patients because teriflunomide may increase exposure of these drugs. (7)

• Rosuvastatin: The dose of rosuvastatin should not exceed 10 mg once daily in patients taking ARAVA. (7)

USE IN SPECIFIC POPULATIONS

• Lactation: Discontinue breastfeeding. (8.2)

• Safety and effectiveness in pediatric patients <12 years of age have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2021

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2.2 Evaluation and Testing Prior to Starting ARAVA

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

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1 INDICATIONS AND USAGE
ARAVA is indicated for the treatment of adults with active rheumatoid arthritis (RA).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose
The recommended dosed of ARAVA is 20 mg once daily. Treatment may be initiated with or without a loading dose, depending upon the patient’s risk of ARAVA-associated hepatotoxicity and ARAVA-associated myelosuppression. The loading dose provides steady-state concentrations more rapidly.

- For patients who are at high risk for ARAVA-associated hepatotoxicity (e.g., those taking concomitant methotrexate) or ARAVA-associated myelosuppression (e.g., patients taking concomitant immunosuppressants), the recommended ARAVA loading dose is 100 mg once daily for 3 days. Subsequently administer 20 mg once daily.
- For patients at high risk for ARAVA-associated hepatotoxicity (e.g., those taking concomitant methotrexate) or ARAVA-associated myelosuppression (e.g., patients taking concomitant immunosuppressants), the recommended ARAVA loading dose is 20 mg once daily without a loading dose.

The maximum recommended daily dose is 20 mg once per day. Consider dosage reduction to 10 mg once daily for patients who are not able to tolerate 20 mg daily (i.e., for patients who experience any adverse events listed in Tables 3 and 4).

Monitor patients carefully after dosage reduction and after stopping therapy with ARAVA, since the active metabolite of leflunomide, teriflunomide, is slowly eliminated from the plasma [see Clinical Pharmacology (12.3)]. After stopping ARAVA treatment, an accelerated drug elimination procedure is recommended to reduce the plasma concentrations of the active metabolite, teriflunomide [see Warnings and Precautions (5.3)]. Without use of an accelerated drug elimination procedure, it may take up to 2 years to reach undetectable plasma teriflunomide concentrations after stopping ARAVA [see Clinical Pharmacology (12.3)].

2.2 Evaluation and Testing Prior to Starting ARAVA
Prior to starting ARAVA treatment, the following evaluations and tests are recommended:
- Evaluate patients for active tuberculosis and screen patients for latent tuberculosis infection [see Warnings and Precautions (5.4)].
- Laboratory tests include alanine aminotransferase (ALT) and white blood cell, hemoglobin or hematocrit, and platelet counts [see Warnings and Precautions (5.2, 5.4, 5.4)].
- For females of reproductive potential, pregnancy testing [see Warnings and Precautions (5.5)].
- Check blood pressure [see Warnings and Precautions (5.10)].

3 DOSAGE FORMS AND STRENGTHS
ARAVA Tablets are available in three strengths:
- Tablets: 10 mg, supplied as white, round film-coated tablet embossed with “ZBN” on one side
- Tablets: 20 mg, supplied as light-yellow, triangular film-coated tablet embossed with “ZBO” on one side
- Tablets: 100 mg, supplied as white, round film-coated tablet embossed with “ZBP” on one side

4 CONTRAINDICATIONS
ARAVA is contraindicated in:
- Pregnant women: ARAVA may cause fetal harm. If a woman becomes pregnant while taking this drug, ARAVA may cause the patient the potential hazard to the fetus, and begin a drug elimination procedure (see Warnings and Precautions (5.5, 5.3, 6.1) and Use in Specific Populations (8.1)).
- Patients with severe hepatic impairment [see Warnings and Precautions (5.2)].
- Patients with known hypersensitivity to leflunomide or any of the other components of ARAVA.
- Known reactions include anaphylaxis and/or angioedema [see Adverse Reactions (6.1)].
- Patients being treated with teriflunomide [see Drug Interactions (7.1)].

5 WARNINGS AND PRECAUTIONS
5.1 Embryo-Fetal Toxicity
ARAVA may cause fetal harm when administered to a pregnant woman. Teratogenicity and embryo-lethality occurred in animal reproduction studies with leflunomide at doses lower than the human exposure level [see Use in Specific Populations (8.1)].

ARAVA is contraindicated for use in pregnant women [see Contraindications (4)]. Exclude pregnancy before starting treatment with ARAVA in females of reproductive potential [see Dosage and Administration (2.2)]. ARAVA therapy of reproductive potential to use effective contraception during ARAVA treatment and during an accelerated drug elimination procedure after ARAVA treatment [see Use in Specific Populations (8.3)]. If a woman becomes pregnant while taking ARAVA, stop treatment with ARAVA, apprise the patient of the potential risk to a fetus, and perform an accelerated drug elimination procedure to achieve non-detectable plasma concentrations of teriflunomide, the active metabolite of leflunomide [see Warnings and Precautions (5.1, 5.3)].

Upon discontinuing ARAVA, it is recommended that all females of reproductive potential undergo an accelerated drug elimination procedure. Women receiving ARAVA treatment who wish to become pregnant must discontinue ARAVA and undergo an accelerated drug elimination procedure, which includes verification that plasma concentrations of the active metabolite, teriflunomide, are less than 0.02 mg/L (0.02 mcg/mL). Based on animal data, human plasma concentrations of teriflunomide of less than 0.02 mg/L (0.02 mcg/mL) are expected to have minimal embryo-fetal risk [see Contraindications (4), Warnings and Precautions (5.3), and Use in Specific Populations (8.1)].

5.2 Hepatotoxicity
Severe liver injury, including fatal liver failure, has been reported in patients treated with ARAVA. An accelerated drug elimination procedure after ARAVA treatment is recommended in patients with cirrhosis, severe hepatic impairment due to hepatic impairment, concomitant use of ARAVA with other potentially hepatotoxic drugs may increase the risk of liver injury. Patients with pre-existing acute or chronic liver disease, or those with serum alanine aminotransferase (ALT) of greater than twice the upper limits of normal (>2 ULN) before initiating treatment, should be treated with caution. Use of ARAVA in patients with acute exacerbation of chronic hepatitis or with active hepatitis within the past year should be avoided. Use of ARAVA in patients with active hepatitis or with active hepatitis within the past year should be avoided. Use of ARAVA in patients with pre-existing acute or chronic liver disease, or those with serum alanine aminotransferase (ALT) of greater than twice the upper limits of normal (>2 ULN) before initiating treatment, should be treated with caution.

5.3 Immunosuppression
Severe liver injury, including fatal liver failure, has been reported in some patients treated with ARAVA. Use of an accelerated drug elimination procedure will rapidly reduce plasma concentrations of leflunomide and its active metabolite, teriflunomide. Therefore, an accelerated elimination procedure should be considered at any time after discontinuation of ARAVA, and in particular, when a patient has experienced a severe adverse reaction (e.g., hepatotoxicity, serious infection, bone marrow suppression, Steven-Johnson Syndrome, toxic epidermal necrolysis, peripheral neuropathy, interstitial lung disease), suspected hypersensitivity, or has become pregnant. It is recommended that all women of childbearing potential undergo an accelerated elimination procedure after stopping ARAVA treatment.

5.4 Immunosuppression, Bone Marrow Suppression, and Risk of Serious Infections
Prior to initiating ARAVA, all patients should be screened for active and inactive (including extra-pulmonary tuberculosis), and aspergillosis. Severe infections including sepsis, which may be fatal, have been reported in patients receiving ARAVA, especially Pneumocystis jirovecii pneumonia and aspergillosis. Most of the reports were confounded by concomitant immunosuppressant therapy and/or comorbid illnesses which, in addition to rheumatoid arthritis, may predispose patients to infection.

Cases of tuberculosis were observed in clinical studies with teriflunomide, the metabolite of ARAVA. Prior to initiating ARAVA, all patients should be screened for active and inactive ("latent") tuberculosis infection, using a commonly used diagnostic test. ARAVA has not been studied in patients with a positive tuberculosis screen, and the safety of ARAVA in individuals with latent tuberculosis infection is unknown.

Patients testing positive in tuberculosis screening should be treated by standard medical practice prior to therapy with ARAVA and monitored carefully during ARAVA treatment for possible reactivation of the infection.

Pancytopenia, agranulocytosis, and thrombocytopenia have been reported in patients receiving ARAVA alone. These events have been reported most frequently in patients who received concomitant treatment with methotrexate or other immunosuppressive agents, or who had recently discontinued those therapies in some cases, patients had a prior history of a significant hematology abnormality. Patients taking ARAVA should have platelet, white blood cell count and hemoglobin or hematocrit monitored at baseline and monthly for six months following initiation of therapy and every 6 to 8 weeks thereafter. If used with concomitant methotrexate and/or other potential immunosuppressive agents, check hemoglobin or hematocrit monthly. If evidence of bone marrow suppression is noted, interrupt ARAVA therapy and treat with other immunosuppressive agents. Use of the accelerated drug elimination procedure may potentially result in return of disease activity if the patient had been responding to ARAVA treatment.

5.5 Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and Drug Reactions with Eosinophilia and Systemic Symptoms
Cases of severe cutaneous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reactions with eosinophilia and systemic symptoms (DRESS) have been reported in patients receiving ARAVA. If a patient taking ARAVA develops any of these conditions, stop ARAVA treatment and perform an accelerated drug elimination procedure to reduce the plasma concentration of the ARAVA active metabolite, teriflunomide [see Warnings and Precautions (5.3)].

In patients in whom the decision is made to switch from ARAVA to another antirheumatic agent with a known potential for hematologic suppression, it would be prudent to monitor for hematologic toxicity, because there will be overlap of systemic exposure to both compounds.

5.6 Malignancy and Lymphoproliferative Disorders
The risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunosuppression medications. There is a potential for immunosuppression with ARAVA. No apparent increase in the incidence of malignancies and lymphoproliferative disorders was reported in the clinical
trials of ARAVA, but larger dosages and longer-term studies would be needed to determine whether there is an increased risk of malignancy or lymphoproliferative disorders with ARAVA.

5.7 Peripheral Neuropathy

Cases of peripheral neuropathy have been reported in patients receiving ARAVA and in clinical studies with teriflunomide, the active metabolite of leflunomide. Most patients recovered after discontinuation of treatment, but some patients had persistent symptoms. Age older than 60 years, concomitant neurotoxic medications, and diabetes may increase the risk for peripheral neuropathy. If a patient taking ARAVA develops a peripheral neuropathy, consider discontinuing ARAVA therapy and performing an accelerated drug elimination procedure. [See Warnings and Precautions (5.3)].

5.8 Interstitial Lung Disease

Interstitial lung disease and worsening of pre-existing interstitial lung disease have been reported during ARAVA therapy, and with normal LFTs, ARAVA was administered to a group of 130 patients starting at 10 mg per day and increased to 20 mg as needed. An increase in ALT greater than or equal to three times the ULN occurred infrequently and reversed with dose reduction or discontinuation of treatment. Table 1 displays the most common adverse reactions in ARAVA-treated patients with RA. The most common adverse reactions in ARAVA-treated patients with RA include diarrhea, elevated liver enzymes, primarily ALT and AST, alopecia, and rash. Table 2 displays the most common adverse reactions in the controlled studies in patients with RA at one year (≥5% in any ARAVA treatment group).

### Table 1: Liver Enzyme Elevations >3-fold Upper Limits of Normal (ULN) in Patients with RA in Trials 1, 2, and 3

<table>
<thead>
<tr>
<th></th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARAVA</td>
<td>PL</td>
<td>ARAVA</td>
</tr>
<tr>
<td></td>
<td>20 mg/day</td>
<td>(n=182)</td>
<td>7.5–15 mg/wk</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3-fold ULN (n %)</td>
<td>8(4.4)</td>
<td>3(2.5)</td>
<td>5(2.7)</td>
</tr>
<tr>
<td>Reversed to ≤2-fold ULN:</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Timing of Elevation</td>
<td>0–3 Months</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4–6 Months</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>7–9 Months</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10–12 Months</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

MTX = methotrexate, PL = placebo, SSZ = sulfasalazine, ULN = Upper limit of normal

*Only 10% of patients in Trial 3 received folate. All patients in Trial 1 received folate.

In a 6 month study of 263 patients with persistent active rheumatoid arthritis despite methotrexate therapy, and with normal LFTs, ARAVA was administered to a group of 130 patients starting at 10 mg per day and increased to 20 mg as needed. An increase in ALT greater than or equal to three times the ULN was observed in 3.8% of patients compared to 0.8% in 133 patients continued on methotrexate placebo.

### Table 2: Percentage Of Patients With Adverse Events ≥5% In Any ARAVA Treated Group in all RA Studies in Patients with RA

<table>
<thead>
<tr>
<th></th>
<th>Placebo-Controlled Trials</th>
<th>Active-Controlled Trials</th>
<th>All RA Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trial 1 and 2</td>
<td>Trial 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARAVA 20 mg/day (n=315)</td>
<td>SSZ 2 g/day (n=133)</td>
<td>ARAVA 20 mg/day (n=501)</td>
</tr>
<tr>
<td></td>
<td>PL (n=210)</td>
<td>MTX 7.5–15 mg/wk (n=182)</td>
<td>MTX 7.5–15 mg/wk (n=498)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27%</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Headache</td>
<td>13%</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13%</td>
<td>11%</td>
<td>19%</td>
</tr>
<tr>
<td>Rash</td>
<td>12%</td>
<td>7%</td>
<td>11%</td>
</tr>
<tr>
<td>Abnormal Liver Enzymes</td>
<td>10%</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>9%</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>9%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>6%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>GI/Abdominal Pain</td>
<td>6%</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5%</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Most common adverse reactions

- Most common adverse reactions in ARAVA-treated patients with RA include diarrhea, elevated liver enzymes (ALT and AST), alopecia, and rash. Table 2 displays the most common adverse reactions in the controlled studies in patients with RA at one year (≥5% in any ARAVA treatment group).
Table 2: Percentage Of Patients With Adverse Events ≥5% In Any ARAVA Treated Group in all RA Studies in Patients with RA (continued)

<table>
<thead>
<tr>
<th></th>
<th>Placebo-Controlled Trials</th>
<th>Active-Controlled Trials</th>
<th>All RA Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trial 1 and 2</td>
<td>Trial 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARAVA 20 mg/day (n=315)</td>
<td>ARAVA 20 mg/day (n=501)</td>
<td>ARAVA (n=1339)†</td>
</tr>
<tr>
<td></td>
<td>PL (n=210)</td>
<td>MTX 7.5–15 mg/wk (n=182)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SSZ 2 g/day (n=133)</td>
<td>MTX 7.5–15 mg/wk (n=498)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>5%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Mouth Ulcer</td>
<td>5%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>2%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| MTX = methotrexate, PL = placebo, SSZ = sulfasalazine
† Only 10% of patients in Trial 3 received folate. All patients in Trial 1 received folate; none in Trial 2 received folate.
†Includes all controlled and uncontrolled trials with ARAVA (duration up to 12 months).
‡Hypertension as a pre-existing condition was overrepresented in all ARAVA treatment groups in phase III trials.

Adverse events during a second year of treatment with ARAVA in clinical trials were consistent with those observed during the first year of treatment and occurred at a similar or lower incidence. Less Common Adverse Reactions

In addition, in controlled clinical trials, the following adverse events in the ARAVA treatment group occurred at a higher incidence than in the placebo group. These adverse events were deemed possibly related to the study drug.

Hypertension was directly administered to the test subjects. Clinical Pharmacology (12.3)

Respiratory: interstitial lung disease, including interstitial pneumonitis and pulmonary fibrosis, which may be fatal, pulmonary hypertension

Skin and Appendages: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis including cutaneous necrotizing vasculitis, cutaneous lupus erythematosus, purpura, vasculitis, or worsening psoriasis, skin ulcer

7 DRUG INTERACTIONS

Following oral administration, leflunomide is metabolized to an active metabolite, teriflunomide, which is responsible for essentially all of leflunomide’s in vivo activity. Drug interaction studies have been conducted with both ARAVA (leflunomide) and with its active metabolite, teriflunomide, where the metabolite was directly administered to the test subjects.

Effect of Potent CYP and Transporter Inducers

Leflunomide is metabolized by CYP450 metabolizing enzymes. Concomitant use of ARAVA and ritampin, a potent inducer of CYP and transporters, increased the plasma concentration of teriflunomide by 40%. However, when coadministered with the metabolite, teriflunomide, ritampin did not affect the pharmacokinetics. No dosage adjustment is recommended for ARAVA when coadministered with ritampin. Because of the potential for ARAVA concentrations to continue to increase with multiple dosing, caution should be used if patients are to be receiving both ARAVA and ritampin [Clinical Pharmacology (12.2)].

Effect on CYP2C8 Substrates

Teriflunomide is an inhibitor of CYP2C8 in vivo. In patients taking ARAVA, exposure of drugs metabolized by CYP2C8 (e.g., paclitaxel, pioglitazone, repaglinide, rosiglitazone) may be increased. Monitor these patients and adjust the dose of the concomitant drug(s) metabolized by CYP2C8 as required [see Clinical Pharmacology (12.3)].

Effect on Warfarin

Coadministration of ARAVA with warfarin requires close monitoring of the international normalized ratio (INR) because teriflunomide, the active metabolite of ARAVA, may decrease peak INR by approximately 25%.

Effect on Oral Contraceptives

Teriflunomide may increase the systemic exposures of ethinyl estradiol and levonorgestrel. Consideration should be given to the type or dose of contraceptives used in combination with ARAVA [see Clinical Pharmacology (12.3)].

Effect on CYP1A2 Substrates

Teriflunomide, the active metabolite of ARAVA, may be a weak inducer of CYP1A2 in vivo. In patients taking ARAVA, exposure of drugs metabolized by CYP1A2 (e.g., alatroxin, duloxetine, theophylline, tizandine) may be reduced. Monitor these patients and adjust the dose of the concomitant drug(s) metabolized by CYP1A2 as required [see Clinical Pharmacology (12.3)].

Effect on Organic Anion Transporter 3 (OAT3) Substrates

Teriflunomide inhibits the activity of OAT3 in vivo. In patients taking ARAVA, exposure of drugs which are OAT3 substrates (e.g., cefaclor, cimetidine, ciprofloxacin, penicillin G, ketoprofen, tamsulosin, methotrexate, zidovudine) may be increased. Monitor these patients and adjust the dose of the concomitant drug(s) which are OAT3 substrates as required [see Clinical Pharmacology (12.3)].

Effect on BCRP and Organic Anion Transporting Polypeptide B1 and B3 (OATP1B1/B3) Substrates

Teriflunomide inhibits the activity of BCRP and OATP1B1/B3 in vivo. For a patient taking ARAVA, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (e.g., midazolam) and drugs in the OATP family (e.g., methotrexate, rifampin), especially HMG-CoA reductase inhibitors (e.g., atorvastatin, pitavastatin, pravastatin, repaglinide, and simvastatin), consider reducing the dose of these drugs and monitor patients closely for signs and symptoms of increased exposures to the drugs while patients are taking ARAVA [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ARAVA during pregnancy. Health care providers and patients are encouraged to report pregnancies by calling 1-877-311-8972 or visit http://www.pregnancyoutcomes.org/participate-in-a-study/

Risk Summary

ARAVA is contraindicated for use in pregnant women because of the potential for fetal harm. In animal reproduction studies, oral administration of leflunomide during organogenesis at a dose of 1/10 of, and equivalent to, the maximum recommended human dose (MRHD) based on AUC, respectively, in rats and rabbits, caused teratogenicity (rats and rabbits), and embryo-larval death (rats) [see Data]. Pregnancy exposure registry data are not available at this time to inform the presence or absence of drug-associated risk with the use of ARAVA during pregnancy.

The background risk of major birth defects and miscarriage for the indicated populations is unknown.

The background risk in the U.S. general population of major birth defects is 2%–4% and of miscarriage is 15%–20% of clinically recognized pregnancies. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, stop treatment with ARAVA, apprise the patient of the potential hazard to a fetus, and perform the accelerated drug elimination procedure to achieve teriflunomide concentrations of less than 0.02 mg/L (0.02 mcg/mL) [see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

Clinical Considerations

Fetal/Neonatal adverse reactions

Lowering the plasma concentration of the active metabolite, teriflunomide, by instituting an accelerated drug elimination procedure as soon as pregnancy is detected may decrease the risk to the fetus from ARAVA. The accelerated drug elimination procedure includes verification that the plasma teriflunomide concentration is less than 0.02 mg/L [see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

Data

Animal data

In an embryo-fetal development study, pregnant rats administered leflunomide during organogenesis from gestation days 7 to 19 at a dose approximately 1/10 of the MRHD (on an AUC basis at a maternal oral dose of 15 mg/kg), teratogenic effects, most notably anophthalmia or microphthalmia and internal hydrophthalmos, were observed. Under these exposure conditions, leflunomide also caused a decrease in the maternal body weight and an increase in embryolethality with a decrease in fetal body weight for surviving fetuses. In an embryo-fetal development study, pregnant rabbits administered leflunomide during organogenesis from gestation days 6 to 18 at a dose approximately equivalent to the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg), a teratogenic finding of fused, dysplastic sternabre was observed. Leflunomide was not teratogenic in rats and rabbits at doses approximately 1/150 and 1/100 of the MRHD, respectively (on an AUC basis at maternal oral dose of 1 mg/kg in both rats and rabbits).

In a pre and postnatal development study, when female rats were treated with leflunomide at a dose that was approximately 1/100 of the MRHD (on an AUC basis at a maternal dose of 1.25 mg/kg) beginning 14 days before mating and continue until the end of lactation, the offspring exhibited marked (greater than 90%) decreases in postnatal survival.
8.2 Lactation
Risk Summary
Clinical lactation studies have not been conducted to assess the presence of ARAVA in human milk, the effects of ARAVA on the breastfed child, or the effects of ARAVA on milk production. Because of the potential for serious adverse reactions in a breastfed infant from ARAVA, advise a nursing woman to discontinue breastfeeding during treatment with ARAVA.

8.3 Females and Males of Reproductive Potential
ARAVA may cause fetal harm when administered during pregnancy. Advise females of the potential risk to the fetus. Advise females to notify their healthcare provider immediately if pregnancy occurs or is suspected during treatment [see Use in Specific Populations (8.1)].

Women receiving ARAVA treatment who wish to become pregnant should discontinue ARAVA and undergo an accelerated drug elimination procedure to achieve plasma teriflunomide concentrations of less than 0.02 mg/L [see Warnings and Precautions (5.3)].

8.4 Pediatric Use
The safety and effectiveness of ARAVA in pediatric patients have not been established.

The safety and effectiveness of ARAVA in the treatment of polyarticular course juvenile idiopathic arthritis (JIA) was evaluated in a single multicenter, double-blind, active-controlled trial in 94 pediatric patients (1:1 randomization) with polyarticular course juvenile idiopathic arthritis (JIA) as defined by the American College of Rheumatology (ACR). In this population, ARAVA treatment was found not to be effective.

The safety of ARAVA was studied in 74 patients with polyarticular course JIA ranging in age from 3–17 years (47 patients from the active-controlled study and 27 from an open-label safety and pharmacokinetic study). The most common adverse events included abdominal pain, diarrhea, nausea, vomiting, oral ulcers, upper respiratory tract infections, alopecia, rash, headache, and dizziness. Less common adverse events included anemia, hypertension, and weight loss. Fourteen pediatric patients experienced ALT and/or AST elevations, nine between 1.2 and 3-fold the upper limit of normal, and five between 3- and 8-fold the upper limit of normal.

8.5 Geriatric Use
Of the total number of subjects in controlled clinical trials (Trials 1, 2, and 3) of ARAVA, 234 subjects were 65 years and over (see Clinical Studies (14)). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment is needed in patients over 65.

8.6 Hepatic Impairment
Dedicated studies of the effect of hepatic impairment on leflunomide pharmacokinetics have not been conducted. Given the need to metabolize leflunomide into the active species, the role of the liver in drug elimination/recycling, and the possible risk of increased hepatic toxicity, the use of ARAVA in patients with hepatic impairment is not recommended.

8.7 Renal Impairment
Dedicated studies of the effect of renal impairment on leflunomide pharmacokinetics have not been conducted. Given that the kidney plays an important role in drug elimination, caution should be used when ARAVA is administered to these patients.

10 OVERDOSAGE
There have been reports of chronic overdose in patients taking ARAVA at daily dose up to five times the recommended daily dose and reports of acute overdose in adults and children. Adverse events were consistent with the safety profile for ARAVA [see Adverse Reactions (6)]. The most frequent adverse events observed were diarrhea, abdominal pain, leukopenia, anemia, and elevated liver function tests. In the event of a significant overdose or toxicity, perform an accelerated drug elimination procedure to accelerate elimination [see Warnings and Precautions (5.3)].

Studies with both hemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that leflunomide is not dialyzable [see Clinical Pharmacology (12.3)].

11 DESCRIPTION
ARAVA (leflunomide) is a pyrimidine synthesis inhibitor. The chemical name for leflunomide is N-(4-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide. It has an empirical formula C₂₃H₁₅F₁₁N₂O₂, a molecular weight of 270.2 and the following structural formula:

\[
\text{CH}_2
\]

ARAVA is available for oral administration as tablets containing 10, 20, or 100 mg of active drug. Combined with leflunomide are the following inactive ingredients: colloidal silica, dioctyl sodium sulfosuccinate, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, starch, talc, titanium dioxide, and yellow ferric oxide (20 mg tablet only).

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Leflunomide is an isoxazole immunomodulatory agent that inhibits dihydroorotate dehydrogenase (a mitochondrial enzyme involved in de novo pyrimidine synthesis) and has antiproliferative activity. Several in vivo and in vitro experimental models have demonstrated an anti-inflammatory effect. Following oral administration, peak teriflunomide concentrations occurred between 6 to 12 hours after dosing. Due to the very long half-life of teriflunomide (18–19 days), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state teriflunomide concentrations. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require about two months of dosing. The resulting plasma concentrations following both loading doses and continued clinical dosing indicate that plasma teriflunomide concentrations are dose proportional.

12.3 Pharmacokinetics
Following oral administration, peak teriflunomide concentrations occurred between 6 to 12 hours after dosing. Due to the very long half-life of teriflunomide (18–19 days), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state teriflunomide concentrations. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require about two months of dosing. The resulting plasma concentrations following both loading doses and continued clinical dosing indicate that plasma teriflunomide concentrations are dose proportional.

Effect of food
Co-administration of leflunomide tablets with a high fat meal did not have a significant impact on teriflunomide plasma concentrations.

Distribution
Teriflunomide is extensively bound to plasma protein (>95%) and is mainly distributed in plasma. The volume of distribution is 11 L after a single intravenous (IV) administration.

Elimination
Teriflunomide, the active metabolite of leflunomide, has a median half-life of 18 to 19 days in healthy volunteers. The elimination of teriflunomide can be accelerated by administration of cholestyramine or activated charcoal. Without use of an accelerated drug elimination procedure, it may take up to 2 years to reach plasma teriflunomide concentrations of less than 0.02 mg/L due to individual variation in drug clearance [see Warnings and Precautions (5.3)]. After a single IV administration of the metabolite (teriflunomide), the total body clearance of teriflunomide was 30.5 ml/h.

Metabolism
In vitro inhibition studies in human liver microsomes suggest that cytochrome P450 (CYP) 1A2, 2C9 and 3A4 are involved in leflunomide metabolism. In vivo, leflunomide is metabolized to one primary (teriflunomide) and many minor metabolites. In vitro, teriflunomide is not metabolized by CYP450 or flavin mononucleotide oxidase enzymes. The parent compound is rarely detectable in plasma.

Excretion
Teriflunomide, the active metabolite of leflunomide, is eliminated by direct bile excretion of unchanged drug as well as renal excretion of metabolites. Over 21 days, 60.1% of the administered dose is excreted in the feces (67.7%) and urine (22.6%). After an accelerated elimination procedure with cholestyramine, an additional 23.1% was recovered (mostly in feces).

Studies with both hemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that teriflunomide is not dialyzable.

Gender
Gender has not been shown to cause a consistent change in the in vivo pharmacokinetics of leflunomide.

Smoking
A population based pharmacokinetic analysis of the clinical trial data indicates that smokers have a 38% increase in clearance over nonsmokers; however, no difference in clinical efficacy was seen between smokers and nonsmokers.

Drug Interaction Studies

Drug interaction studies have been conducted with both ARAVA (leflunomide) and with its active metabolite, teriflunomide, where the metabolite was directly administered to the test subjects.

The potential effect of other drugs on ARAVA has been assessed.

Potent CYP and transporter inhibitors:

Following coadministration of a single dose of ARAVA to subjects receiving multiple doses of rifampin, teriflunomide peak concentrations were increased (~40%) over those seen when ARAVA was given alone [see Drug Interactions (7)].

An in vivo interaction study with ARAVA and cimetidine (nonspecific weak CYP inhibitor) has demonstrated a lack of a significant impact on teriflunomide exposure.

The potential effect of ARAVA on other drugs:

CYP2C8 Substrates
There was an increase in mean repaglinide Cₘₐₓ and AUC (1.7 and 2.4-fold, respectively), following repeated doses of teriflunomide and a single dose of 0.25 mg repaglinide, suggesting that teriflunomide is an inhibitor of CYP2C8 in vivo. The magnitude of interaction could be higher at the recommended repaglinide dose [see Drug Interactions (7)].

CYP1A2 Substrates
Repeated doses of teriflunomide decreased mean Cₘₐₓ and AUC of caffeine by 18% and 55%, respectively, suggesting that teriflunomide may be a weak inducer of CYP1A2 in vivo.

CYP3A4 Substrates
There was an increase in mean cefazolin Cₘₐₓ and AUC (1.43 and 1.54-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of organic anion transporter 3 (OAT3) in vivo [see Drug Interactions (7)].

BCRP and OATP1B1/3 Substrates
There was an increase in mean rosuvastatin Cₘₐₓ and AUC (2.6 and 2.51-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of BCRP transporter and organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1/3) [see Drug Interactions (7)].

Oral Contraceptives
There was an increase in mean ethinylestradiol Cₘₐₓ and AUC (1.58 and 1.54-fold, respectively), and levonorgestrel Cₘₐₓ and AUC (1.33 and 1.41-fold, respectively) following repeated doses of teriflunomide [see Drug Interactions (7)].

Teriflunomide did not affect the pharmacokinetics of bupropion (a CYP2B6 substrate), midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), omeprazole (a CYP2C19 substrate), and metoprolol (a CYP2D6 substrate).
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of leflunomide up to the maximally tolerated dose of 6 mg/kg (approximately 1/40 of the maximum human teriflunomide systemic exposure based on AUC). However, male mice in a 2-year bioassay exhibited an increased incidence in lymphoma at an oral dose of 15 mg/kg, the highest dose studied (1.7 times the human teriflunomide exposure based on AUC). Female mice, in the same study, exhibited a dose-related increased incidence of bronchoalveolar adenomas and carcinomas combined beginning at 1.5 mg/kg (approximately 1/10 the human teriflunomide exposure based on AUC). The significance of the findings in mice relative to the clinical use of ARAVA is not known. Leflunomide was not mutagenic in the Ames assay, the unscheduled DNA synthesis assay, or in the HGPSRT gene mutation assay. In addition, leflunomide was not clastogenic in the in vivo mouse micronucleus assay or in the in vivo Chinese hamster bone marrow cell cytogenic test. However, 4-terifluoromethylalanine (TFMA), a minor metabolite of leflunomide, was mutagenic in the Ames assay and in the HGPSRT gene mutation assay, and was clastogenic in the in vitro Chinese hamster cell chromosomal aberration assay. TFMA was not clastogenic in the in vivo mouse micronucleus assay or in the in vivo Chinese hamster bone marrow cytogenic test.

Leflunomide had no effect on fertility or reproductive performance in either male or female rats at oral doses up to 4.0 mg/kg (approximately 1/30 the human teriflunomide exposure based on AUC) [see Use in Specific Populations (8.1, 8.6)].

14 CLINICAL STUDIES
The efficacy of ARAVA in the treatment of rheumatoid arthritis (RA) was demonstrated in three controlled trials showing reduction in signs and symptoms, and inhibition of structural damage. In two placebo controlled trials, efficacy was demonstrated for improvement in physical function. In these trials, efficacy was evaluated by:
1. Reduction of signs and symptoms
   Relief of signs and symptoms was assessed using the American College of Rheumatology (ACR) 20 Responder Index, a composite of clinical, laboratory, and functional measures in rheumatoid arthritis. An "ACR20 Responder" is a patient who had ≥20% improvement in both tender and swollen joint counts and in 3 of the following 5 criteria: physician global assessment, patient global assessment, functional ability measure (Modified Health Assessment Questionnaire [MHAQ]), visual analog scale, and erythrocyte sedimentation rate or C-reactive protein. An "ACR20 Responder at Endpoint" is a patient who completed the study and was an ACR20 Responder at the completion of the study.
2. Inhibition of structural damage
   Inhibition of structural damage compared to control was assessed using the Sharp score, a composite score of x-ray erosions and joint space narrowing in hands/wrists and forefoot.
3. Improvement in physical function
   Improvement in physical function was assessed using the Health Assessment Questionnaire (HAQ) and the Medical Outcomes Survey Short Form (SF-36).
   In all ARAVA trials, participants of at least 18 years of age and in ARA-functional class of I, II, or III received an initial loading dose of 100 mg leflunomide per day for three days, followed by 20 mg per day thereafter.
   Exclusion criteria included patients with a history of hypersensitivity to the study medication; women who were pregnant or breastfeeding and men or women of child bearing age and potential who had not received contraceptives for at least 4 weeks before entering the study and to be maintained throughout the study and for at least 6 months after discontinuing treatment; patients with a history of inflammatory disease, impaired renal function or liver impairment, cardiac failure, congenital or acquired immunodeficiency, impaired coagulation, or a history of recent major traumatic injury; and patients taking intra-articular or systemic concomitant medications which could affect the safety and/or efficacy of the study medication.

Trial 1
Trial 1, a 2-year study, randomized 482 patients with active RA of at least 6 months duration to leflunomide 20 mg/day (n=182), methotrexate 7.5 mg/week increasing to 15 mg/week (n=182), or placebo (n=118). All patients received folate 1 mg BID. The primary analysis was at 52 weeks with 96 weeks of follow-up.

Trial 2
Trial 2 randomized 358 patients with active RA to leflunomide 20 mg/day (n=133), sulfasalazine 2.0 g/day (n=133), or placebo (n=92). Treatment duration was 24 weeks. An extension of the study was an optional 6-month blinded continuation of Trial 2 without the placebo arm, resulting in a 12-month comparison of leflunomide and sulfasalazine.

Of the 168 patients who completed 12 months of treatment, 146 patients (87%) entered a 1-year extension study of double-blind active treatment (60 leflunomide, 60 sulfasalazine, 26 placebo/sulfasalazine). Leflunomide dose continued at 20 mg/day and the methotrexate dose could be increased to a maximum of 20 mg/week. In total, 190 patients (83 leflunomide, 80 methotrexate, 36 placebo) continued into a second 12 months of double-blind treatment.

Trial 3
Trial 3 randomized 999 patients with active RA to leflunomide 20 mg/day (n=301) or methotrexate at 7.5 mg/week increasing to 15 mg/week (n=498). Folate supplementation was used in 10% of patients. Treatment duration was 52 weeks. Of the 736 patients who completed 52 weeks of treatment in study Trial 3, 612 (83%) entered the double-blind, 1-year extension study (232 leflunomide, 320 methotrexate). Patients continued on the same daily dosage of leflunomide or methotrexate that they had been taking at the completion of Trial 2. A total of 121 patients (53 leflunomide, 47 sulfasalazine, 21 placebo/sulfasalazine) completed the 2 years of double-blind treatment.

Clinical Trial Results
Clinical response
The ACR20 Responder at Endpoint rates are shown in Figure 1. ARAVA was statistically significantly superior to placebo in reducing the signs and symptoms of RA by the primary efficacy analysis. ACR20 Responder at Endpoint, in study Trial 1 (at the primary 12 months endpoint) and Trial 2 (at 6 month endpoint), ACR20 Responder at Endpoint rates with ARAVA treatment were consistent across the 6 and 12 months studies (41%–49%). No consistent differences were demonstrated between leflunomide and methotrexate or between leflunomide and sulfasalazine. ARAVA treatment effect was evident by 1 month, stabilized by 3 to 6 months, and continued throughout the course of treatment as shown in Figure 1.

Figure 1: Percentage of ACR20 Responders at Endpoint in Patients with Active RA in Trials 1, 2, and 3

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARAVA vs Placebo (12, 32)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Methotrexate vs Placebo (8, 30)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>ARAVA vs Methotrexate (-4, 16)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARAVA vs Placebo (7, 33)</td>
<td>0.0026</td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine vs Placebo (4, 29)</td>
<td>0.0121</td>
<td></td>
</tr>
<tr>
<td>ARAVA vs Sulfasalazine (-6, 16)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Trial 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARAVA vs Methotrexate (-10, -7)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2: ACR20 Responders over Time in Patients with Active RA in Trial 1*

*Last Observation Carried Forward.

ACR20 and ACR70 Responders are defined in an analogous manner to the ACR 20 Responder, but use improvements of 50% or 70%, respectively (Table 3). Mean change for the individual components of the ACR Responder Index are shown in Table 4.

Table 3: Summary of ACR Response Rates in Patients with Active RA in Trials 1, 2, and 3

<table>
<thead>
<tr>
<th>Study and Treatment Group</th>
<th>ACR20</th>
<th>ACR50</th>
<th>ACR70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-Controlled Studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 1 (12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| ARAVA (n=178)
| 52
| 34
| 20
| Placebo (n=119)
| 26
| 8
| 4
| Methotrexate (n=180)
| 46
| 23
| 9


*Note: ACR20 and ACR70 Responder rates are defined in a manner analogous to the ACR 20 Responder, but use improvements of 50% or 70%, respectively. Mean change for the individual components of the ACR Responder Index are shown in Table 4.
Table 3: Summary of ACR Response Rates in Patients with Active RA in Trials 1, 2, and 3 (continued)

<table>
<thead>
<tr>
<th>Study and Treatment Group</th>
<th>ACR20</th>
<th>ACR50</th>
<th>ACR70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 2 (6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARAVA (n=130)†</td>
<td>55‡</td>
<td>33‡</td>
<td>10§</td>
</tr>
<tr>
<td>Placebo (n=91)†</td>
<td>29</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Sulfasalazine (n=132)†</td>
<td>57</td>
<td>30</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 4: Mean Change in the Components of the ACR Responder Index in Patients with Active RA in Trials 1, 2, and 3

<table>
<thead>
<tr>
<th>Components</th>
<th>Placebo-Controlled Studies</th>
<th>Non–Placebo-Controlled Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trial 1 (12 months)</td>
<td>Trial 2 Non-US (6 months)</td>
</tr>
<tr>
<td></td>
<td>Leflunomide</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Tender joint count†</td>
<td>-7.7</td>
<td>-6.6</td>
</tr>
<tr>
<td>Swollen joint count†</td>
<td>-5.7</td>
<td>-5.4</td>
</tr>
<tr>
<td>Patient global assessment‡</td>
<td>-2.1</td>
<td>-1.5</td>
</tr>
<tr>
<td>Physician global assessment‡</td>
<td>-2.8</td>
<td>-2.4</td>
</tr>
<tr>
<td>Physical function/disability (MHAQ/HAQ)</td>
<td>-0.29</td>
<td>-0.15</td>
</tr>
<tr>
<td>Pain intensity‡</td>
<td>-2.2</td>
<td>-1.7</td>
</tr>
<tr>
<td>Erythrocyte Sedimentation rate</td>
<td>-6.26</td>
<td>-6.48</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>-0.62</td>
<td>-0.50</td>
</tr>
</tbody>
</table>

Not included in the ACR Responder Index

| Morning Stiffness (min)         | -101.4      | -88.7      | 14.7    | -93.0       | -42.4       | -6.8    | -63.7       | -86.6       |

*Last Observation Carried Forward; Negative Change Indicates Improvement
†Based on 28 joint count
‡Visual Analog Scale - 0=Best; 10=Worst

Maintenance of effect

After completing 12 months of treatment, patients continuing on study treatment were evaluated for an additional 12 months of double-blind treatment (total treatment period of 2 years). ACR Responder rates at 12 months were maintained over 2 years in most patients continuing a second year of treatment. Improvement from baseline in the individual components of the ACR responder criteria was also sustained in most patients during the second year of ARAVA treatment in all three trials.

Radiographic Response

The change from baseline to endpoint in progression of structural disease, as measured by the Sharp x-ray score, is displayed in Figure 3. ARAVA was statistically significantly superior to placebo in inhibiting the progression of disease by the Sharp score. No consistent differences were demonstrated between leflunomide and methotrexate or between leflunomide and sulfasalazine.

Figure 3: Change in Sharp Score in Patients with Active RA in Trials 1, 2, and 3
Comparisons | 95% Confidence Interval | p Value
---|---|---
**Trial 1**
ARAVA vs Placebo | (-4.0, -1.1) | 0.0007
Methotrexate vs Placebo | (-2.6, -0.2) | 0.0196
ARAVA vs Methotrexate | (-2.3, 0.0) | 0.0499
**Trial 2**
ARAVA vs Placebo | (-6.2, -1.8) | <0.0001
Sulfasalazine vs Placebo | (-6.9, 0.0) | 0.0484
ARAVA vs Sulfasalazine | (-3.3, 1.2) | NS
**Trial 3**
ARAVA vs Methotrexate | (-2.2, 7.4) | NS

**Physical Function Response**
The Health Assessment Questionnaire (HAQ) assesses a patient's physical function and degree of disability. The mean change from baseline in functional ability as measured by the HAQ Disability Index (HAQ DI) in the 6 and 12-month placebo and active-controlled trials is shown in Figure 4. ARAVA was statistically significantly superior to placebo in improving physical function. Superiority to placebo was demonstrated consistently across all eight HAQ DI subscales (dressing, arising, eating, walking, hygiene, reach, grip, and activities) in both placebo controlled studies.

The Medical Outcomes Survey Short Form 36 (SF-36), a generic health-related quality of life questionnaire, further addresses physical function. In Trial 1, at 12 months, ARAVA provided statistically significant improvements compared to placebo in the Physical Component Summary (PCS) Score.

**Maintenance of effect**
The improvement in physical function demonstrated at 6 and 12 months was maintained over two years. In those patients continuing therapy for a second year, this improvement in physical function as measured by HAQ and SF-36 (PCS) was maintained.

<table>
<thead>
<tr>
<th>Strength</th>
<th>Quantity</th>
<th>NDC Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>30 count bottle</td>
<td>0088-2190-30</td>
<td>White, round film-coated tablet embossed with “ZBN” on one side.</td>
</tr>
<tr>
<td>20 mg</td>
<td>30 count bottle</td>
<td>0088-2161-30</td>
<td>Light yellow, triangular film-coated tablet embossed with “ZBO” on one side.</td>
</tr>
</tbody>
</table>