These highlights do not include all the information needed to use Leflunomide safely and effectively. See full prescribing information for Leflunomide.

Initial U.S. Approval: 1998

WARNING: EMBRYO-FETAL TOXICITY and HEPATOTOXICITY

See full prescribing information for complete boxed warning.

Embryo-Fetal Toxicity

- Teratogenicity and embryo-kidney toxicity occurred in animals administered leflunomide (5.1, 8.1).
- Exclude pregnancy prior to initiating leflunomide 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)

Hepatotoxicity

- Severe liver injury and fatal liver failure have been reported. (5.2)
- Avoid leflunomide use in patients with pre-existing liver disease, or those with serum alanine aminotransferase (ALT) >2×ULN. (5.2, 8.6)

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 ethinylestradiol and levonorgestrel. 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 rosvastatin should not exceed 10 mg once daily in patients taking leflunomide. (7)

INDICATIONS AND USAGE

Leflunomide 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 leflunomide-associated hepatotoxicity and leflunomide-associated myelosuppression: 100 mg daily for 3 days. (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 leflunomide. (2.2)

Dosage Forms and Strengths

Tablets: 10 mg, 20 mg. (3)

WARNINGS AND PRECAUTIONS

- After stopping leflunomide, 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), pancreatitis, agranulocytosis and thrombocytopenia: Stop leflunomide and use accelerated elimination procedure. Do not start leflunomide in patients with active infection. Monitor CBCs during treatment with leflunomide. (5.4)
- Stevens-Johnson syndrome and toxic epidermal necrolysis: Stop leflunomide and use accelerated elimination procedure. (5.5)
- Peripheral neuropathy: If patient develops symptoms consistent with peripheral neuropathy, evaluate patient and consider discontinuing leflunomide. (5.7)
- Intestinal lung disease: May be fatal. New onset or worsening symptoms may necessitate discontinuation of leflunomide 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 leflunomide treatment were diarrhea, respiratory infection, nausea, headache, rash, abnormal liver enzymes, dyspepsia. (6.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2016
Leflunomide is contraindicated for use in pregnant women because of the potential for fetal harm. Teratogenicity and embryo-lethality occurred in animal reproduction studies with leflunomide at doses lower than the human exposure level. Exclude pregnancy before the start of treatment with leflunomide in females of reproductive potential. Advise females of reproductive potential to use effective contraceptive during leflunomide treatment and during an accelerated drug elimination procedure after leflunomide treatment. Stop leflunomide and use an accelerated drug elimination procedure if the patient becomes pregnant. [see Contraindications (4), Warnings and Precautions (5.1, 5.3), Use in Special Populations (8.1, 8.3), and Clinical Pharmacology (12.3)]

5.3 Procedure for Accelerated Elimination of Leflunomide and its Active Metabolite

The active metabolite of leflunomide, teriflunomide, is eliminated slowly from the plasma [see Clinical Pharmacology (12.3)]. 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 leflunomide, and prior to conception if a patient has experienced a severe adverse reaction (e.g., hepatotoxicity, serious infection, bone marrow suppression, Stevens-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 without stopping leflunomide treatment.

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, the plasma concentration not associated with embryo-fetal toxicity in animals. Elimination can be accelerated by the following procedures: 1) Administer cholestyramine 8 grams orally 3 times daily for 11 days. 2) Alternatively, administer 50 grams of activated charcoal powder [made into a suspension orally] every 12 hours for 11 days. Verify plasma teriflunomide concentrations of less than 0.02 mg/L (0.02 µg/mL) by two separate tests at least 14 days apart. If plasma teriflunomide concentrations are higher than 0.02 mg/L, repeat oral cholestyramine and/or activated charcoal administration.

The duration of accelerated drug elimination treatment may be modified based on the clinical status and tolerability of the elimination procedure. The procedure may be repeated as needed, based on teriflunomide concentrations and clinical status.

Use of the accelerated drug elimination procedure may potentially result in return of disease activity if the patient had been responding to leflunomide treatment.

5.4 Immunosuppression, Bone Marrow Suppression, and Risk of Serious Infections

Leflunomide is not recommended for patients with severe immunodeficiency, bone marrow dysplasia, or uncontrolled infections, or who have had a serious infection or have become pregnant. It is recommended that all women of childbearing potential undergo an accelerated drug elimination procedure and initiating the accelerated drug elimination procedure [see Warnings and Precautions (5.3)]. Medications like leflunomide that have immunosuppression potential may cause patients to be more susceptible to infections, including opportunistic infections, especially Pneumocystis jiroveci pneumonia (PJP), and concomitant tuberculin testing may be useful. Patients who have a history of tuberculosis infection are at higher risk. Cases of tuberculosis were observed in clinical studies with teriflunomide, the metabolite of leflunomide. Prior to initiating leflunomide, all patients should be screened for active and inactive ("latent") tuberculosis infection as per commonly used diagnostic tests. Leflunomide has not been studied in patients with a positive tuberculin screen, and the safety of leflunomide in individuals with latent tuberculosis infection is unknown. Patients testing positive in tuberculin screening should be treated by standard medical practice prior to therapy with leflunomide and monitored carefully during leflunomide treatment for possible reactivation of the infection. Pneumonia, agranulocytosis and agranulocytosis-like syndromes have been reported in patients receiving leflunomide 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 these therapies; in some cases, patients had a prior history of a significant hematologic abnormality. Patients taking leflunomide 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, consider interrupting the leflunomide therapy and investigate the cause. If likely leflunomide-induced, perform the accelerated drug elimination procedure and monitor liver tests weekly until normalized [see Warnings and Precautions (5.3)]. If teriflunomide-induced liver injury is unlikely because some other cause has been found, resumption of leflunomide therapy may be considered.

If leflunomide and methotrexate are given concomitantly, follow the American College of Rheumatology (ACR) guidelines for monitoring methotrexate liver toxicity with ALT, AST, and serum albumin testing.

5.5 Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and Drug Reactions with Anaphylaxis

Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients receiving leflunomide. If a patient taking leflunomide develops any of these conditions, stop leflunomide treatment and perform an accelerated drug elimination procedure [see Warnings and Precautions (5.3)].

FULL PRESCRIBING INFORMATION

WARNINGS AND PRECAUTIONS (5.3)

Up to 2 years to reach undetectable plasma teriflunomide concentrations after stopping leflunomide treatment. Stop leflunomide and use an accelerated drug elimination procedure if the patient becomes pregnant. [see Contraindications (4), Warnings and Precautions (5.1, 5.3), Use in Special Populations (8.1, 8.3), and Clinical Pharmacology (12.3)]

5.2 Hepatotoxicity

Severe liver injury, including fatal liver failure, has been reported in some patients treated with leflunomide. Patients with pre-existing acute or chronic liver disease, or those with serum alanine aminotransferase (ALT) >2xULN before initiating treatment, are at increased risk and should not be treated with leflunomide. Monitor ALT levels at least monthly for six months after starting leflunomide, and thereafter every 6-8 weeks. If leflunomide-induced liver injury is suspected, stop leflunomide treatment, start an accelerated drug elimination procedure, and monitor liver tests weekly until normalized. [see Contraindications (4), Warnings and Precautions (5.2, 5.3), Use in Special Populations (8.6)]
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 leflunomide. No apparent increase in the incidence of malignancies and lymphoproliferative disorders was reported in the clinical trials of leflunomide, but larger dosages and longer-term studies would be needed to determine whether there is an increased risk of malignancy or lymphoproliferative disorders with leflunomide.

5.7 Peripheral Neuropathy

Cases of peripheral neuropathy have been reported in patients receiving leflunomide 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 symptoms, such as cough and dyspnea, with or without associated fever, may be a reason for discontinuation of leflunomide therapy and performing an accelerated drug elimination procedure [see Dosage and Administration (5.3)].

5.8 Interstitial Lung Disease

Interstitial lung disease and worsening of pre-existing interstitial lung disease have been reported during treatment with leflunomide and has been associated with fatal outcomes [see Adverse Reactions (6.2)]. The risk of leflunomide-associated interstitial lung disease is increased in patients with a history of interstitial lung disease. Interstitial lung disease is a potentially fatal disorder that may occur acutely at any time during therapy and has a variable clinical presentation. New onset or worsening pulmonary symptoms, such as cough and dyspnea, with or without associated fever, may be a reason for discontinuation of leflunomide therapy and for further investigation as appropriate. If discontinuation of leflunomide is necessary, consider performing an accelerated drug elimination procedure [see Warnings and Precautions (5.3)]

5.9 Vaccinations

No clinical data are available on the efficacy and safety of vaccinations during Leflunomide treatment. Vaccination with live vaccines is, however, not recommended. The long half-life of the active metabolite of leflunomide should be considered when contemplating administration of a live vaccine after stopping leflunomide.

5.10 Blood Pressure Monitoring

In placebo-controlled studies with the active metabolite of leflunomide, teriflunomide, elevations in blood pressure were observed in some subjects. Blood pressure should be checked before starting treatment with leflunomide and monitored periodically thereafter [See Adverse Reactions (6.1)].

6. ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:
- Hepatotoxicity [see Warnings and Precautions (5.2)]
- Immunosuppression [see Warnings and Precautions (5.4)]
- Bone marrow suppression [see Warnings and Precautions (5.4)]
- Stevens-Johnson syndrome and toxic epidermal necrolysis [see Warnings and Precautions (5.5)]
- Peripheral neuropathy [see Warnings and Precautions (5.7)]
- Interstitial lung disease [see Warnings and Precautions (5.8)]

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In clinical studies (Trials 1, 2, and 3), 1,865 patients were treated with leflunomide administered as either monotherapy or in combination with methotrexate or sulfasalazine. Patients ranged in age from 19 to 85 years, with an overall median age of 58 years. The mean duration of RA was 6 years ranging from 0 to 45 years.

Elevation of Liver Enzymes

Treatment with leflunomide was associated with elevations of liver enzymes, primarily ALT and AST, in a significant number of patients; these effects were generally reversible. Most transaminase elevations were mild (≥ 2-fold ULN) and usually resolved while continuing treatment. Marked elevations (≥ 3-fold ULN) occurred infrequently and reversed with dose reduction or discontinuation of treatment. Table 1 shows liver enzyme elevations seen with monthly monitoring in clinical trials Trial 1 and Trial 2. It was notable that the absence of folate use in Trial 3 was associated with a considerably greater incidence of liver enzyme elevation on methotrexate.

### 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>Timing of Elevation</th>
<th>ALT (n=182)</th>
<th>PL (n=118)</th>
<th>MTX (n=182)</th>
<th>ALT (n=201)</th>
<th>PL (n=133)</th>
<th>SSZ (n=201)</th>
<th>ALT (n=498)</th>
<th>MTX (n=498)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 Months</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>4-6 Months</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>7-9 Months</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>10-12 Months</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>6</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, leflunomide 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 0.6% in 133 patients continued on methotrexate with placebo.

#### Most Common Adverse Reactions

The most common adverse reactions in leflunomide-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 leflunomide treatment group).

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

<table>
<thead>
<tr>
<th>Placebo-Controlled Trials</th>
<th>Active-Controlled Trials</th>
<th>All RA Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial 1 and 2</strong></td>
<td><strong>Trial 3</strong></td>
<td><strong>Trial 3</strong></td>
</tr>
<tr>
<td><strong>LEFLUNOMIDE 20 mg/day</strong> (N=210)</td>
<td>PL (N=210)</td>
<td>SSZ (N=133)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27%</td>
<td>4%</td>
</tr>
<tr>
<td>Headache</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>Rash</td>
<td>12%</td>
<td>2%</td>
</tr>
<tr>
<td>Abnormal Liver Enzymes</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>GI/Abdominal Pain</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5%</td>
<td>4%</td>
</tr>
</tbody>
</table>
Table 2. Percentage Of Patients With Adverse Events ≥5% In Any Leflunomide 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>Leflunomide 20 mg/day (N=215)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PL (N=210)</td>
<td>5%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>SSZ 2.0 g/day (N=133)</td>
<td>5%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>MTX 7.5 – 15 mg/wk (N=182)</td>
<td>6%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Leflunomide 20 mg/day (N=501)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX 7.5 – 15 mg/wk (N=496)</td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Leflunomide (N=1329)†</td>
<td>1%</td>
<td>1%</td>
<td>3%</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 leflunomide (duration up to 12 months).
‡Hypertension as a preexisting condition was overrepresented in all leflunomide treatment groups in phase III trials.

Adverse events during a second year of treatment with leflunomide 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 leflunomide treatment group occurred at a higher incidence than in the placebo group. These adverse events were deemed possibly related to the study drug.

#### Blood and Lymphatic System
- Neutropenia
- Eosinophilia
- Anemia
- Thrombocytopenia
- Leukopenia

#### Cardiac System
- Arrhythmia
- Chest pain

#### Gastrointestinal System
- Diarrhea
- Gastroparesis
- Gastritis
- Nausea
- Vomiting
- Flatulence
- Abdominal pain

#### General Disorders
- Anorexia
- Weight loss

#### Hematologic System
- Thrombocytopenia
- Thrombocytosis

#### Liver and Biliary System
- Liver disease
- Hepatitis

#### Musculoskeletal System
- Myalgia
- Arthralgia
- Osteoporosis

#### Respiratory System
- Pharyngitis
- Voice disorder

### Skin and Appendages
- Rash
- Erythema
- Urticaria
- Pruritus

### Nervous System
- Dizziness
- Headache
- Insomnia
- Drowsiness

### Immune System
- Hypersensitivity reactions
- Anaphylaxis
- Proteinuria

### Infection
- Upper respiratory tract infection
- Urinary tract infection

### General Disorders
- Malaise
- Fatigue
- Muscle weakness

### In vivo Activity

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

### Effect on CYP and Transporter Inducers

Leflunomide is metabolized by CYP3A4 and CYP2C8. Concomitant use of leflunomide and rifampin, a potent inducer of CYP and transporters, increased the plasma concentration of teriflunomide by 40%. However, when co-administered with the metabolite, leflunomide, rifampin did not affect its pharmacokinetics. No dosage adjustment is recommended for leflunomide when coadministered with rifampin. Because of the potential for leflunomide concentrations to continue to increase with multiple dosing, caution should be used if patients are to be receiving both leflunomide and rifampin [see Clinical Pharmacology (12.3)].

#### Effect on CYP2C8 substrates

Teriflunomide is an inhibitor of CYP2C8 in vivo. In patients taking leflunomide, exposure of drugs metabolized by CYP2C8 (e.g., paxil, citalopram, escitalopram, duloxetine) may be increased. Teriflunomide, the active metabolite of leflunomide, may be a weak inducer of CYP1A2 [see Clinical Pharmacology (12.3)].

#### Effect on BCRP and OAT3 substrates

The following additional adverse reactions have been identified during postapproval use of leflunomide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Drug interaction studies have been conducted with both leflunomide and with its active metabolite, teriflunomide, where the metabolite was directly administered to the test subjects.

#### Effect on CYP3A4 substrates

The accelerated drug elimination procedure includes teriflunomide, by its metabolite, and by infliximab. The accelerated drug elimination procedure includes the plasma teriflunomide concentration is less than 0.02 mg/L [see Warnings and Precautions (5.3)].

### Clinical Considerations

#### Fetal/Neonatal adverse reactions

Lowering the plasma concentration of the active metabolite, leflunomide, by instituting an accelerated drug elimination procedure as soon as pregnancy is detected may decrease the risk to the fetus from leflunomide. The accelerated drug elimination procedure includes teriflunomide, by its metabolite, and by infliximab. The accelerated drug elimination procedure includes 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 embryofetal 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 dose of 15 mg/kg), teratogenic effects, the most notable anophthalmia or microphthalmia and internal hydrocephalus, 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 embryofetal 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 ears was observed. Leflunomide was not teratogenic in rats and rabbits at doses above 1/10 and 1/10 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 post-natal 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 continuing until the end of lactation, the offspring exhibited marked (greater than 90%) decreases in postnatal survival.

#### Pregnancy

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

#### Risk Summary

Leflunomide 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-lethality (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 the concomitant drug(s) which are OAT3 substrates as required [see Clinical Pharmacology (12.3)].

#### Pregnancy Exposure Registry

In a pre- and post-natal 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, the most notable anophthalmia or microphthalmia and internal hydrocephalus, 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 embryofetal 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 ears was observed. Leflunomide was not teratogenic in rats and rabbits at doses above 1/10 and 1/10 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 post-natal 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 continuing until the end of lactation, the offspring exhibited marked (greater than 90%) decreases in postnatal survival.
is responsible for essentially all of leflunomide’s metabolism. Following oral administration, leflunomide is metabolized to an active metabolite, teriflunomide, which is responsible for essentially all of leflunomide’s metabolism.

8.3 Females and Males of Reproductive Potential

Leflunomide should be avoided during pregnancy or when breastfeeding (see Drug Interactions (7) and Use in Specific Populations (8.1)). Use of active treatment of leflunomide is recommended in women for whom expectations of pregnancy are unlikely or have been excluded by appropriate tests. If the benefit of leflunomide outweighs the risks, there are no known adverse congenital effects of leflunomide. Use of a medically approved contraceptive is strongly recommended in women of child-bearing potential before treatment with leflunomide begins. If conception occurs during treatment, the patient should be informed of the potential for fetal harm, with the severity of the congenital malformations depending on the dose of leflunomide at the time of conception. The safety of leflunomide in pregnancy has not been established. Leflunomide may be present in breast milk, but the effects of leflunomide on the breastfed child, or the effects of leflunomide on milk production, have not been 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.

8.4 Pediatric Use

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Leflunomide is an oxazole immunomodulatory agent that inhibits dihydroorotate dehydrogenase (a mitochondrial enzyme involved in de novo pyrimidine synthesis) and has antiinflammatory activity. Several in vivo and in vitro experimental models have demonstrated an antiinflammatory effect.

12.2 Pharmacokinetics

Following oral administration, leflunomide is metabolized to an active metabolite, teriflunomide, which is responsible for essentially all of leflunomide’s in vivo activity. Plasma concentrations of the parent drug, leflunomide, have been occasionally seen at very low concentrations. Studies of the pharmacokinetics of leflunomide have primarily examined the plasma concentrations of the active metabolite, teriflunomide.

Absorption

Following oral administration, peak teriflunomide concentrations occurred between 6–12 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. 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 18–19 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 clearances [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.

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

Specific Populations

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

Effect of Food

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

Drug Interaction Studies

Drug interaction studies have been conducted with both leflunomide and with its active metabolite, teriflunomide, where the metabolite was directly administered to the test subjects. The Potential Effect of Other Drugs on Leflunomide

• Polymorphonuclear leukocyte inducers: Following concomitant administration of a single dose of leflunomide to subjects receiving multiple doses of rifampin, teriflunomide peak concentrations were increased (~40%) over those seen when leflunomide was given alone [see Drug Interactions (7)].

• In vivo interaction study with leflunomide and cimetidine (non-specific weak CYP inhibitor) has demonstrated a lack of significant impact on teriflunomide exposure.

The Potential Effect of Leflunomide 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.

• OAT3 Substrates

There was an increase in mean cetoril 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 OATP1B1/1B3 Substrates

There was an increase in mean rosuvastatin Cmax and AUC (2.65- 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 (OATP1B1/1B3) [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 the maximum human terflunomide 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 leflunomide is not known.

Leflunomide was not mutagenic in the Ames assay, the unscheduled DNA synthesis assay, or in the HGPRT gene mutation assay. In addition, leflunomide was not clastogenic in the in vivo mouse micronuclease assay or in the in vivo Chinese hamster bone marrow cell cytogenetic test. However, 4-trifluoromethylaniline (TFMA), a minor metabolite of leflunomide, was mutagenic in the Ames assay and in the HGPRT 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 micronuclease assay or in the in vivo Chinese hamster bone marrow cell cytogenetic 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 leflunomide 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 pain 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 forefeet.

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 leflunomide trials, participants of at least 18 years of age and in ARA functional class of I, II or III received an initial loading dosage 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 breast-feeding 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; patients taking intra-articular or systemic concomitant medications which could affect the safety and/or efficacy of the study medication.

**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). Participants received folic acid 1 mg BID. The primary analysis was at 52 weeks with blinded treatment to 104 weeks.
- Overall, 235 of the 508 randomized patients (47%) entered a 12 month double-blind treatment group (86 leflunomide, 101 methotrexate, 68 placebo). 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, 37 placebo) completed 2 years of double-blind treatment.

**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: (80 leflunomide, 60 sulfasalazine, 26 placebo/sulfasalazine). Patients continued on the same daily dosage of leflunomide or sulfasalazine 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.

**Trial 3**

- Randomized 999 patients with active RA to leflunomide 20 mg/day (n=501) 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 739 patients who completed 52 weeks of treatment in study Trial 3, 612 (83%) entered the double-blind, 1-year extension study (292 leflunomide, 320 methotrexate). Patients continued on the same daily dosage of leflunomide or methotrexate that they had been taking at the completion of Trial 3. There were 553 patients (236 leflunomide, 277 methotrexate) who completed 2 years of double-blind treatment.

**Clinical Trial Results**

The ACR20 Responder at Endpoint rates are shown in Figure 1. Leflunomide 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 leflunomide treatment were consistent across the 6 and 12 month studies (41 – 49%). No consistent differences were demonstrated between leflunomide and methotrexate or between leflunomide and sulfasalazine. Leflunomide treatment effect was evident by 1 month, stabilized by 3 – 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>Trial</th>
<th>Comparison</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>Leflunomide vs. Placebo</td>
<td>12,32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Methotrexate vs. Placebo</td>
<td>8,30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Leflunomide vs. Methotrexate</td>
<td>-4,16</td>
<td>NS</td>
</tr>
<tr>
<td>Trial 2</td>
<td>Leflunomide vs. Placebo</td>
<td>7,33</td>
<td>0.0026</td>
</tr>
<tr>
<td></td>
<td>Sulfasalazine vs. Placebo</td>
<td>4,29</td>
<td>0.0121</td>
</tr>
<tr>
<td></td>
<td>Leflunomide vs. Sulfasalazine</td>
<td>-8,16</td>
<td>NS</td>
</tr>
<tr>
<td>Trial 3</td>
<td>Leflunomide vs. Methotrexate</td>
<td>-19,-7</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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

*Last Observation Carried Forward.

ACR50 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>
<tr>
<td>Leflunomide (n=178)†</td>
<td>52‡</td>
<td>34‡</td>
<td>20‡</td>
</tr>
<tr>
<td>Placebo (n=118)†</td>
<td>26</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Methotrexate (n=185)†</td>
<td>46</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>Trial 2 (6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leflunomide (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>
<tr>
<td>Non-Placebo Active-Controlled Studies</td>
<td></td>
<td></td>
<td></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>Leflunomide Methotrexate Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tender joint count†</td>
<td>-7.7 -6.6 -3.0</td>
<td>-9.7 -8.1 -4.3</td>
</tr>
<tr>
<td>Swollen joint count†</td>
<td>-5.7 -5.4 -2.9</td>
<td>-7.2 -6.2 -3.4</td>
</tr>
<tr>
<td>Patient global assessment‡</td>
<td>-2.1 -1.5 0.1</td>
<td>-2.8 -2.6 -0.9</td>
</tr>
<tr>
<td>Physician global assessment‡</td>
<td>-2.8 -2.4 -1.0</td>
<td>-2.7 -2.5 -0.8</td>
</tr>
<tr>
<td>Physical function/disability (MHAQ/HAQ)</td>
<td>-0.29 -0.15 0.07</td>
<td>-0.50 -0.29 -0.04</td>
</tr>
<tr>
<td>Pain intensity‡</td>
<td>-2.2 -1.7 -0.5</td>
<td>-2.7 -2.0 -0.9</td>
</tr>
<tr>
<td>Erythrocyte Sedimentation rate</td>
<td>-6.26 -6.48 2.56</td>
<td>-7.48 -16.56 3.44</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>-0.62 -0.50 0.47</td>
<td>-2.26 -1.19 0.16</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
§Not included in the ACR Responder Index

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 leflunomide 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. Leflunomide 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

<table>
<thead>
<tr>
<th>Trial 1</th>
<th>Leflunomide vs. Placebo</th>
<th>(-4.5, -1.1)</th>
<th>0.0007</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methotrexate vs. Placebo</td>
<td>(-2.6, -0.2)</td>
<td>0.0196</td>
</tr>
<tr>
<td></td>
<td>Leflunomide vs. Methotrexate</td>
<td>(-2.3, 0.0)</td>
<td>0.0499</td>
</tr>
<tr>
<td>Trial 2</td>
<td>Leflunomide vs. Placebo</td>
<td>(-6.2, -1.8)</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>Sulfasalazine vs. Placebo</td>
<td>(-6.9, 0.0)</td>
<td>0.0484</td>
</tr>
<tr>
<td></td>
<td>Leflunomide vs. Sulfasalazine</td>
<td>(-3.3, 1.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Trial 3</td>
<td>Leflunomide vs. Methotrexate</td>
<td>(-2.2, 7.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

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. Leflunomide 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, leflunomide provided statistically significant improvements compared to placebo in the Physical Component Summary (PCS) Score.
**Figure 4. Change in Functional Ability Measure in Patients with Active RA in Trials 1, 2, and 3**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leflunomide vs. Placebo</td>
<td>(-0.58, -0.29)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Leflunomide vs. Methotrexate</td>
<td>(-0.34, -0.07)</td>
<td>0.0026</td>
</tr>
<tr>
<td><strong>Trial 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leflunomide vs. Placebo</td>
<td>(-0.67, -0.36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leflunomide vs. Sulfasalazine</td>
<td>(-0.33, -0.03)</td>
<td>0.0163</td>
</tr>
<tr>
<td><strong>Trial 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leflunomide vs. Methotrexate</td>
<td>(0.01, 0.16)</td>
<td>0.0221</td>
</tr>
</tbody>
</table>

**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.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**How Supplied**

**Leflunomide Tablets**

<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>0955-1735-30</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>0955-1737-30</td>
<td>Light yellow, triangular film-coated tablet embossed with “ZBO” on one side.</td>
</tr>
</tbody>
</table>

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Protect from light.

**17 PATIENT COUNSELING INFORMATION**

**Embryo-Fetal Toxicity**

Advisors females of reproductive potential:

- Of the potential for fetal harm if leflunomide is taken during pregnancy.
- To notify their healthcare provider immediately if a pregnancy occurs or is suspected.
- To use effective contraception during therapy with leflunomide and until the active metabolite (teriflunomide) plasma concentration is verified to be less than 0.02 mg/L [see Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.3)].

**Pregnancy Exposure Registry**

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to leflunomide during pregnancy [see Use in Specific Populations (8.1)].

**Lactation**

Advisors nursing women to discontinue breastfeeding during treatment with leflunomide [see Use in Specific Populations (8.2)].

Advisors patients of the possibility of rare, serious skin reactions. Instruct patients to promptly report if they develop a skin rash or mucous membrane lesions.

Advisors patients of the potential hepatotoxic effects of leflunomide and of the need for monitoring liver enzymes. Instruct patients to report if they develop symptoms such as unusual tiredness, abdominal pain or jaundice.

Advisors patients that they may develop a lowering of their blood counts and should have frequent hematologic monitoring. This is particularly important for patients who are receiving other immunosuppressive therapy concurrently with leflunomide, who have recently discontinued such therapy before starting treatment with leflunomide, or who have had a history of a significant hematologic abnormality. Instruct patients to promptly report if they notice symptoms consistent with pancytopenia, such as easy bruising or bleeding, recurrent infections, fever, paleness or unusual tiredness.