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

**LEFLUNOMIDE tablets, for oral use**

**WARNING:** EMBRYO-FETAL TOXICITY and HEPATOTOXICITY

See full prescribing information for complete boxed warning.

**Embryo-Fetal Toxicity**
- Teratogenicity and embryo-lethality 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)
- Stop leflunomide 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 leflunomide use in patients with pre-existing liver disease, or those with serum alanine aminotransferase (ALT) >2 × ULN. (5.2, 8.6)
- Use caution when leflunomide is given with other potentially hepatotoxic drugs. (5.2)
- Monitor ALT levels. Interrupt leflunomide 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**

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

**DOSE 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)
- 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 leflunomide. (2.2)

**DOSE 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), pancytopenia, 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, drug reaction with eosinophilia and systemic symptoms (DRESS): 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)
- Interstitial 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)

**CONTRAINDICATIONS**

- Pregnancy (4, 5.1, 8.1)
- Severe hepatic impairment. (4, 5.2)
- Hypersensitivity to leflunomide or any of its inactive components. (4)
- Current teriflunomide treatment. (4)

**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 rosvustatin should not exceed 10 mg once daily in patients taking leflunomide. (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: 04/2022
Warnings and Precautions (5.3)

4 CONTRAINDICATIONS

Leflunomide may cause fetal harm when administered to a pregnant woman. Teratogenicity and embryo-lethality occurred in animal studies performed with leflunomide 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 contraception 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 Specific Populations (8.1, 8.3), and Clinical Pharmacology (12.3)].

Hepatotoxicity

Severe liver injury, including fatal liver failure, has been reported in patients treated with leflunomide. Leflunomide is contraindicated in patients with severe hepatic impairment. Concomitant use of leflunomide 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 transaminase (ALT) >2 × ULN 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 to 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 Specific Populations (8.6)].

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

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 contraception 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 Specific 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 transaminase (ALT) >2 × ULN 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 to 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 Warnings and Precautions (5.3)]. If leflunomide-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.

5.3 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 discontinuance of leflunomide, and in particular, when a patient has experienced a severe adverse reaction (e.g., hepatotoxicity, serious infection, bone marrow suppression, Stevens-Johnson Syndrome, toxic epidermal necrolysis, peripheral neuropathy, intestinal lung disease), suspected hypersensitivity, or has become pregnant. It is recommended that all women of childbearing potential undergo an accelerated elimination procedure after 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 mgL, the plasma concentration not associated with embryo-fetal toxicity in animals.

Elimination can be accelerated by the following procedures:

1. Administer cholestyramine 6 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 mgL (0.02 μg/mL) by two separate tests at least 14 days apart. If plasma teriflunomide concentrations are higher than 0.02 mgL, repeat cholestyramine and/or activated charcoal treatment.

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 depression, or severe, uncontrolled infections. Monitor patients with a positive tuberculosis screen, and the safety of leflunomide in individuals with latent tuberculosis infection is unknown. Patients testing positive in tuberculosis screening should be treated to standard medical practice prior to therapy with leflunomide and monitored carefully during leflunomide treatment for possible reactivation of the infection.

Fluvoxamine, aripiprazole, and clozapine 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 monitoring platelet count weekly and/or every 6 to 8 weeks. If evidence of bone marrow suppression occurs in a patient taking leflunomide, stop treatment with leflunomide and perform an accelerated drug elimination procedure to reduce the plasma concentration of the leflunomide active metabolite, teriflunomide [see Warnings and Precautions (5.3)].

In any situation in which the decision is made to switch from leflunomide to another antirheumatic agent, due to potential for hematologic suppression, it would be prudent to monitor for hematologic toxicity, because there will be overlap of systemic exposure to both compounds.

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

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)].
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 neurotic medications, and diabetes may increase the risk for peripheral neuropathy. If a patient taking leflunomide develops a peripheral neuropathy, consider discontinuing leflunomide therapy and performing an accelerated drug elimination procedure [see Warnings and Precautions (5.7)].

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 (5.8)].

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, PARTICULARLY 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></th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Leflunomide 20 mg/day (n=118)</td>
<td>PL (n=118)</td>
<td>MTX 7.5–15 mg/wk (n=182)</td>
</tr>
<tr>
<td>ALT (SGPT) &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 &lt;2-fold ULN:</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

Timing of Elevation

<table>
<thead>
<tr>
<th></th>
<th>0–3 Months</th>
<th>4–6 Months</th>
<th>7–9 Months</th>
<th>10–12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leflunomide 20 mg/day (n=315)</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>MTX (n=182)</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PL (n=118)</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SSZ 2 g/day (n=133)</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Leflunomide 20 mg/day (n=201)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>MTX 7.5–15 mg/wk (n=498)</td>
<td>-</td>
<td>6</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, 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 0.8% 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></th>
<th>Placebo-Controlled Trials</th>
<th>Active-Controlled Trials</th>
<th>All RA Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1 and 2</td>
<td>Leflunomide 20 mg/day (n=210)</td>
<td>PL (n=201)</td>
<td>SSZ 2 g/day (n=133)</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>Atherosia</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>
</tbody>
</table>
Effect on Warfarin directly administered to the test subjects. Conducted with both leflunomide and with its active metabolite, teriflunomide, where the metabolite was required

Pharmacology (12.3)

Monitor these patients and adjust the dose of the concomitant drug(s) metabolized by CYP2C8 as is responsible for essentially all of leflunomide’s activity. 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 leflunomide and with its active metabolite, teriflunomide, where the metabolite was

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: leukocytosis, thrombocytopenia Cardiovascular: chest pain, palpitation, thrombophlebitis of the leg, varicose vein Eye: blurred vision, eye disorder, papilledema, retinal disorder, retinal hemorrhage Gastrointestinal: alkaline phosphatase increased, anorexia, bilirubinemia, flatulence, gamma-GT increased, salivary gland enlarged, sore throat, vomiting, dry mouth General Disorders: malaise Immune System: anaphylactic reaction Infection: abscess, flu syndrome, vaginal moniliasis Nervous System: dizziness, headache, somnolence Respiratory System: dyspnea

6.2 Postmarketing Experience

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. Blood and Lymphatic System: agranulocytosis, leukopenia, neutropenia, pancytopenia Infection: opportunistic infections, severe infections including sepsis Gastrointestinal: acute hepatic necrosis, colitis, including microscopic colitis, hepatitis, jaundice/ cholestasis, pancreatitis, severe liver injury such as hepatic failure Immune System: angioedema Nervous system: peripheral neuropathy 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, purpuric pemphigus 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 leflunomide and with its active metabolite, teriflunomide, where the metabolite was directly administered to the test subjects. Effect of Potent CYP and Transporter Inhibitors Leflunomide is metabolized by CYP2C8 metabolizing enzymes. Concomitant use of leflunomide and rifampin, a potent inducer of CYP and transporters, increased the plasma concentration of teriflunomide by 40%. However, when coadministered with the metabolite, teriflunomide, rifampin did not affect its pharmacokinetics. No dosage adjustment is recommended for leflunomide when coadministered with rifampin. Because of the potential for leflunomide concentration to increase 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., 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 leflunomide with warfarin requires close monitoring of the international normalized ratio (INR) because teriflunomide, the active metabolite of leflunomide, may decrease peak INR by approximately 25%. Effect on Oral Contraceptives Teriflunomide may increase the systemic exposures of ethinylestradiol and levonorgestrel. Consideration should be given to the type or dose of contraceptives used in combination with leflunomide [see Clinical Pharmacology (12.3)].

Effect on CYP1A2 Substrates

Teriflunomide, the active metabolite of leflunomide, may be a weak inducer of CYP1A2 in vivo. In patients taking leflunomide, exposure of drugs metabolized by CYP1A2 [e.g., allopurinol, diltiazem, disulfiram, fluconazole, lansoprazole, nefazodone, nefazodone, phenytoin, prucalopride, rosiglitazone, such as phenytoin, teriflunomide, zidovudine] may be increased. Monitor these patients and adjust the dose of the concomitant drug(s) 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 leflunomide, exposure of drugs which are OAT3 substrates (e.g., cefaclor, cimetidine, ciprofloxacin, pencillin G, ketoprofen, furosemide, metformin, salicylates, and sulfonamides) may be increased. Monitor these patients and adjust the dose of the concomitant drug(s) as required [see Clinical Pharmacology (12.3)].

Effect on BCRP and Organic Anion Transporting Polypeptide B1 and B3 (OATP/B1/B3). Substances Teriflunomide inhibits the activity of BCRP and OATP/B1/B3 in vivo. For a patient taking leflunomide, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (e.g., mitoxantrone) and drugs in the OATP family (e.g., metformin, ritanserin), also HMG-CoA reductase inhibitors (e.g., atorvastatin, rosuvastatin, 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 leflunomide [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 leflunomide during pregnancy. Healthcare 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 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-fetal 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 leflunomide during pregnancy. The background risk for 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%–25% of clinically recognized pregnancies. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, stop treatment with leflunomide, 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 (5.2) and Clinical Considerations].

Ceftioral 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 teriflunomide. 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)].

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 10 mg/kg), a teratogenic finding of fused, dysplastic sternebrae was observed. Leflunomide was not teratogenic in rats and rabbits at doses approximately 1/150 and 1/10 of the MRHD, respectively (on an AUC basis at maternal oral dose of 1 mg/kg in both rats and rabbits).

Table 2: Percentage Of Patients With Adverse Events ≥5% In Any Leflunomide Treated Group in all RA Studies in Patients with RA (continued)

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<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>Abdominal Pain</td>
<td>5%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>5%</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5%</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Mouth Ulcer</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5%</td>
<td>2%</td>
<td>4%</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>1%</td>
</tr>
</tbody>
</table>

MTX = methotrexate, PL = placebo, SSZ = sulphasalazine

* Only 10% of patients in Trial 3 received folic acid. All patients in Trial 1 received folic acid; none in Trial 2 received folic acid.

† 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.
In a pre and postnatal development study, when female rats were treated with leflunomide at a dose that was approximately 1150 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.

8.2 Lactation
Risk Summary
Clinical lactation studies have not been conducted to assess the presence of leflunomide in human milk, the effects of leflunomide on the breastfed child, or the effects of leflunomide on milk production. Because of the potential for serious adverse reactions in a breastfed infant from leflunomide, advise a nursing woman not to breastfeed during treatment with leflunomide.

8.3 Females and Males of Reproductive Potential
Leflunomide 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 leflunomide treatment who wish to become pregnant should discontinue leflunomide and undergo a transmitted drug elimination procedure to achieve plasma teriflunomide concentrations of less than 0.02 mg/L (0.02 mcg/mL) (see Warnings and Precautions [5.3]).

Pregnancy Testing
Exclude pregnancy in females of reproductive potential before starting treatment with leflunomide.

Contraception
Females
Advise females of reproductive potential to use effective contraception during treatment with leflunomide and while undergoing a drug elimination procedure until verification that the plasma teriflunomide concentration is less than 0.02 mg/L (see Warnings and Precautions [5.3]).

8.4 Pediatric Use
The safety and effectiveness of leflunomide in pediatric patients have not been established. The safety and effectiveness of leflunomide 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, leflunomide treatment was found not to be effective.

The safety of leflunomide 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 leflunomide, 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 age to be a factor influencing the selection of patients for treatment with leflunomide. However, greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment is needed in patients over 65.

8.6 Hepatic Impairment
Studies conducted in vivo in liver microsomes suggest that cytochrome P450 (CYP) 1A2, 1A2, 2C9, 2C19, 3A4 and 3A5 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 monoxygenase enzymes.

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8.7 Renal Impairment
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Contraception
Females
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Contraception
Females
Advise females of reproductive potential to use effective contraception during treatment with leflunomide and while undergoing a drug elimination procedure until verification that the plasma teriflunomide concentration is less than 0.02 mg/L (see Warnings and Precautions [5.3]).
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 teriflunomide systemic exposure based on AUC). However, male mice in a 2-year bioassay exhibited an increased incidence in lymphomas at an oral dose of 15 mg/kg, the highest dose studied (1.7 times the human teriflunomide systemic 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 micronucleus assay or in the in vivo Chinese hamster bone marrow cell cytogenic test. However, 4-trifluoromethylaminoanthranilic acid (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 micronucleus assay or in the in vivo Chinese hamster bone marrow cell 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 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 (RA). 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 feet/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 leflunomide 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, 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 treatment effect being 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

Trial 1 Leflunomide vs Placebo (12, 32) p<0.0001
Methotrexate vs Placebo (8, 30) p<0.0001
Leflunomide vs Methotrexate (-4, 16) NS

Trial 2 Leflunomide vs Placebo (7, 33) p=0.0026
Sulfasalazine vs Placebo (4, 29) 0.0121
Leflunomide vs Sulfasalazine (-8, 16) NS
Leflunomide vs Methotrexate (-19, -7) p<0.0001

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

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>
<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=180)</td>
<td>46</td>
<td>23</td>
<td>9</td>
</tr>
</tbody>
</table>

*Last Observation Carried Forward.
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>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>
<tr>
<td>Trial 3 (12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leflunomide (n=495)†</td>
<td>51</td>
<td>31</td>
<td>10</td>
</tr>
</tbody>
</table>

*Intent to treat (ITT) analysis using last observation carried forward (LOCF) technique for patients who discontinued early.
†n is the number of ITT patients for whom adequate data were available to calculate the indicated rates.
‡p < 0.001 leflunomide vs placebo
§p < 0.02 leflunomide vs placebo

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>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 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>Trials</th>
<th>Leflunomide vs Placebo</th>
<th>Methotrexate vs Placebo</th>
<th>Leflunomide vs Methotrexate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>(-4.0, -1.1)</td>
<td>(-2.6, -0.2)</td>
<td>(-2.3, 0.0)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>(-6.2, -1.8)</td>
<td>(-6.9, 0.0)</td>
<td>(-3.3, 1.2)</td>
</tr>
<tr>
<td>Trial 3</td>
<td>(-2.2, 7.4)</td>
<td></td>
<td></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.

![Change in Sharp Score](image.png)
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>Trial 1 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>Trial 2 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>Trial 3 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°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light.

17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity
Advise 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 treatment 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), and 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
Advise nursing women to discontinue breastfeeding during treatment with leflunomide [see Use in Specific Populations (8.2)].

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

Investigations
• Advise 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.
• Advise 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.
• Inform patients about the early warning signs of interstitial lung disease and ask them to contact their physician promptly if these symptoms appear or worsen during therapy.

Manufactured for:
Winthrop U.S.,
a business of sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
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