Product Monograph

Including Patient Medication Information

[Pr]APO-LEFLUNOMIDE

Leflunomide Tablets

For oral use

10 mg and 20 mg of leflunomide

Apotex Standard

Antirheumatic, Immunomodulator Agent

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Date of Authorization:
2026-05-15

Control Number: 501186

Recent Major Label Changes

7 Warnings and Precautions, Perioperative Considerations	2025-09
7 Warnings and Precautions, Skin	2025-09
7 Warnings and Precautions, Skin	2026-05
7 Warnings and Precautions, Musculoskeletal	2026-05

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Recent Major Label Changes 2

Table of Contents 2

Part 1: Healthcare Professional Information 5

1 Indications 5

1.1 Pediatrics 5

1.2 Geriatrics 5

2 Contraindications 5

4 Dosage and Administration 6

4.2 Recommended Dose and Dosage Adjustment 6

4.4 Administration 7

4.5 Missed Dose 7

5 Overdose 7

6 Dosage Forms, Strengths, Composition, and Packaging 8

7 Warnings and Precautions 8

General 8

Carcinogenesis and Genotoxicity 9

Cardiovascular 10

Gastrointestinal 10

Hematologic 11

Hepatic/Biliary/Pancreatic 11

Immune 13

Monitoring and Laboratory Tests 13

Musculoskeletal 14

Neurologic....15
Perioperative Considerations....15
Renal....15
Reproductive Health....15
Respiratory....17
Skin....18
7.1 Special Populations....18
7.1.1 Pregnancy....18
7.1.2 Breastfeeding....18
7.1.3 Pediatrics....19
7.1.4 Geriatrics....19
8 Adverse Reactions....19
8.1 Adverse Reaction Overview....19
8.2 Clinical Trial Adverse Reactions....19
8.3 Less Common Clinical Trial Adverse Reactions....22
8.5 Post-Market Adverse Reactions....23
9 Drug Interactions....24
9.2 Drug Interactions Overview....24
9.4 Drug-Drug Interactions....25
9.5 Drug-Food Interactions....30
9.6 Drug-Herb Interactions....30
9.7 Drug-Laboratory Test Interactions....30
10 Clinical Pharmacology....30
10.1 Mechanism of Action....30
10.3 Pharmacokinetics....31
11 Storage, Stability, and Disposal....33
Part 2: Scientific Information....34
13 Pharmaceutical Information....34
14 Clinical Trials....34
14.1 Clinical Trials by Indication....34

14.2 Comparative Bioavailability Studies 42

15 Microbiology 44

16 Non-Clinical Toxicology 44

17 Supporting Product Monographs 62

Patient Medication Information 63

Part 1: Healthcare Professional Information

1 Indications

APO-LEFLUNOMIDE (leflunomide) should be used only by physicians who have fully familiarized themselves with the efficacy and safety profile of APO-LEFLUNOMIDE and who are experienced in the therapy of rheumatoid diseases.

APO-LEFLUNOMIDE is indicated in adults for the treatment of active rheumatoid arthritis.

1.1 Pediatrics

The use in patients less than 18 years of age is contraindicated.

1.2 Geriatrics

No dosage adjustment is needed in patients over 65 years of age. There are no overall differences in effectiveness and safety between elderly and younger patients.

2 Contraindications

APO-LEFLUNOMIDE is contraindicated in:

- Patients with known hypersensitivity to APO-LEFLUNOMIDE (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme), to teriflunomide or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.
- Patients with immunodeficiency states, due to causes other than rheumatoid arthritis (e.g., AIDS) (see 7 Warnings and Precautions, Immune).
- Patients with impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid arthritis.
- Patients with serious infections.
- Patients with moderate to severe renal insufficiency because the kidney plays a role in the elimination of leflunomide.
- Patients with impairment of liver function (APO-LEFLUNOMIDE in monotherapy or in combination with other hepatotoxic drugs e.g., Disease Modifying Antirheumatic Drugs [DMARDs] such as methotrexate) given the possible risk of increased hepatotoxicity and the role of the liver in activation, elimination and recycling of leflunomide (see 9.4 Drug-Drug Interactions).

While the mechanism of action of leflunomide and methotrexate are different, their pharmacodynamic action of interfering with cell division is similar. Concomitant treatment with methotrexate and/or other liver and bone marrow toxic medications is associated with an increased risk of serious hepatic or marrow reactions and requires strict vigilance in monitoring

(see 7 Warnings and Precautions, Monitoring and Laboratory Tests).

If a switch in treatment from leflunomide to another hepatotoxic DMARD is required, the washout and monitoring must be adhered to as mentioned in the 7 Warnings and Precautions, Monitoring and Laboratory Tests and General, Washout procedures).

- Patients with severe hypoproteinemia (e.g., in nephrotic syndrome). Since the active metabolite of leflunomide, A771726, is highly protein-bound and cleared via hepatic metabolism and biliary secretion.

- Pregnant women, or women of childbearing potential who are not using reliable contraception before, during, and for a period of two years after treatment with APO-LEFLUNOMIDE (or as long as the plasma levels of the active metabolite are above 0.02 mg/L). Pregnancy must be excluded before start of treatment with APO-LEFLUNOMIDE (see 7.1.1 Pregnancy).

- Women who are breast feeding (see 7.1.2 Breastfeeding).

- Patients less than 18 years of age (see 7.1.3 Pediatrics).

Male patients should be aware of the possible male-mediated foetal toxicity. Reliable contraception during treatment with APO-LEFLUNOMIDE should also be guaranteed (see 7 Warnings and Precautions, Reproductive Health and 7.1.1 Pregnancy).

4 Dosage and Administration

4.2 Recommended Dose and Dosage Adjustment

Loading Dose
Due to the long half-life in patients with rheumatoid arthritis and recommended dosing interval (24 hr), a loading dose is needed to yield steady-state concentrations more rapidly. It is recommended that APO-LEFLUNOMIDE therapy be initiated with a loading dose of 100 mg per day for 3 days.

Maintenance Therapy
Daily dosing of 20 mg is recommended for treatment of patients with rheumatoid arthritis. A small cohort of patients (n=104) treated with 25 mg/day experienced a greater incidence of side effects: alopecia, weight loss, liver enzyme elevations. Doses higher than 20 mg/day are not recommended. If dosing at 20 mg/day is not well tolerated clinically, the dose may be decreased to 10 mg daily. Due to the prolonged half-life of the active metabolite of APO-LEFLUNOMIDE, patients should be carefully observed after dose reduction since it may take several weeks for metabolite levels to decline (see 7 Warnings and Precautions, Monitoring and Laboratory Tests).

A treatment effect may be evident after 4 weeks and may further improve up to 4 to 6 months after start of treatment.

Geriatrics (≥ 65 years) No dosage adjustment is needed in patients over 65 years of age.

Pediatrics (< 18 years)
The use in patients less than 18 years of age is contraindicated.

Patients with Renal Impairment

Because the kidney plays a role in the elimination of leflunomide, and without sufficient studies of the use of leflunomide in patients with renal insufficiency, caution should be used when considering the administration of APO-LEFLUNOMIDE to patients with mild renal insufficiency (see 2 Contraindications).

4.4 Administration

APO-LEFLUNOMIDE tablets should be swallowed whole, with sufficient liquid. APO-LEFLUNOMIDE can be taken with or without food, without regard to meals, at the same time everyday.

4.5 Missed Dose

If the patient forgot to take a tablet of APO-LEFLUNOMIDE they should be advised to take it as soon as they remember, unless it is nearly time for their next dose. The patient should be advised not to double-up on the next dose to make up for the missed dose.

5 Overdose

There have been reports of chronic overdose in patients taking leflunomide at daily doses up to five times the recommended daily dose and reports of acute overdose in adults or children. The majority of the reported overdoses were without adverse events. In cases where adverse events were reported, they were consistent with the safety profile for leflunomide (see 8 Adverse Reactions). The most frequent adverse events observed were diarrhea, abdominal pain, leucopenia, anemia and elevated liver function tests.

In the event of relevant overdose or toxicity, cholestyramine or activated charcoal administration is recommended.

Cholestyramine given orally at a dose of 8 g three times a day for 24 hours to three healthy volunteers decreased plasma levels of A771726 by approximately 40% in 24 hours and by 49 to 65% in 48 hours (see 7 Warnings and Precautions, General, Washout Procedures).

Administration of activated charcoal (powder made into a suspension) orally or via nasogastric tube (50 g every 6 hours for 24 hours) has been shown to reduce plasma concentrations of the active metabolite, A771726, by 37% in 24 hours and by 48% in 48 hours.

These washout procedures may be repeated if clinically necessary.

Studies with both hemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that A771726, the primary metabolite of leflunomide, is not dialyzable.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/Strength/Composition	Non-Medicinal Ingredients
oral	Tablets 10 mg and 20 mg	Anhydrous lactose, colloidal silicon dioxide, crospovidone and magnesium stearate.

APO-LEFLUNOMIDE is available for oral administration as tablets containing 10 and 20 mg of leflunomide.

APO-LEFLUNOMIDE 10 mg Tablets: Each white, round, biconvex tablet, engraved "LE" over "10" and "APO" on the other side, contains 10 mg leflunomide. Available in bottles of 30 and 100.

APO-LEFLUNOMIDE 20 mg Tablets: Each white, arc triangular, biconvex tablet, engraved "LE" over "20" and "APO" on the other side" contains 20 mg leflunomide. Available in bottles of 30 and 100.

7 Warnings and Precautions

General

The active metabolite of leflunomide, A771726, has a long half-life. Serious undesirable effects might occur and persist (e.g. hepatotoxicity, hematotoxicity or allergic reactions, see below), even if the treatment with APO-LEFLUNOMIDE has been stopped. For the management of the above-mentioned toxicities a washout procedure should be performed.

If a severe adverse reaction to leflunomide occurs, or if for any other reason A771726 needs to be cleared rapidly from the body, cholestyramine or activated charcoal has to be initiated and continued/repeated as clinically necessary (see 5 Overdose). For suspected severe

immunologic/allergic reactions, more prolonged cholestyramine or activated charcoal administration may be necessary to achieve rapid and sufficient clearance (see below the Washout Procedures).

Similarly, when switching to another DMARD (e.g. methotrexate) after treatment with APO-LEFLUNOMIDE a washout procedure should be performed since there exist a possibility of additive risks of adverse events for a long time after the switching (see below the Washout Procedures and see also the 2 Contraindications and 9.4 Drug-Drug Interactions).

Recent treatment with hepatotoxic DMARDs may result in increased side effects; therefore, the initiation of APO-LEFLUNOMIDE treatment has to be carefully considered regarding these benefit/risk aspects. Caution and careful monitoring of liver and bone marrow function is necessary if these drugs are used concomitantly (see 2 Contraindications and 9.4 Drug-Drug Interactions).

Co-administration of teriflunomide with APO-LEFLUNOMIDE is not recommended, since it will lead to an increase in the plasma exposure of A771726 in an additive manner, as APO-LEFLUNOMIDE is the parent compound of teriflunomide.

Interruption of APO-LEFLUNOMIDE treatment, administering a washout procedure, should be considered in the peri-surgical period due to effects on impaired wound healing (see 7 Warnings and Precautions, Perioperative Considerations and Skin).

Washout Procedures

One of the following is recommended to achieve a fast decrease in plasma levels after stopping treatment with APO-LEFLUNOMIDE:

1) 8 g cholestyramine 3 times daily for 11 days OR

2) 50 g activated charcoal 4 times daily for 11 days

The duration may be modified depending on clinical or laboratory variables.

Similarly low A771726 plasma levels may be expected 2 years after stopping APO-LEFLUNOMIDE without one of the above washout methods. Due to individual variation in drug clearance, some patients may decrease to below this plasma level in less time (e.g., 6 months).

For information regarding measurements of A771726, please contact Apotex Inc.

Carcinogenesis and Genotoxicity

Malignancy

The risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of

some immunosuppressive medications. There is a potential for immunosuppression with APO-LEFLUNOMIDE. No apparent increase in the incidence of malignancies and lymphoproliferative disorders was reported in the clinical trials of leflunomide, but larger and longer-term studies would be needed to determine whether there is an increased risk of malignancies or lymphoproliferative disorders with leflunomide.

Carcinogenesis, and Mutagenesis

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 A771726 systemic exposure based on the area under the curve [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 A771726 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 A771726 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 nor in the *in vivo* Cytogenetic Test in Chinese Hamster Bone Marrow Cells. However, 4-trifluoromethylanaline (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* Assay for Chromosome Aberrations in the Chinese Hamster Cells. TFMA was not clastogenic in the *in vivo* Mouse Micronucleus Assay nor in the *in vivo* Cytogenetic Test in Chinese Hamster Bone Marrow Cells.

Cardiovascular

In addition to hypertension noted in Clinical Trials, isolated reports of difficulty with blood pressure control including cases of malignant hypertension and hypertensive crisis have been submitted. Although a causal relationship to leflunomide has not been established and confounding factors were present in most cases, it is considered essential that monitoring recommendations are closely followed (see 7 Warnings and Precautions, Monitoring and Laboratory Tests).

Serious cases of pulmonary hypertension, some with a fatal outcome, have been reported post-marketing in patients treated with Leflunomide. The majority of these cases have been reported in patients with underlying heart disease, valvular disorders, lung disorders (ILD), and pulmonary thromboembolism. Caution should be exercised when leflunomide is used in patients with heart disease, valvular disorders, lung disorders (ILD), or pulmonary thromboembolism.

Gastrointestinal

Post marketing cases of colitis including ulcerative, microscopic colitis and Crohn's Disease, have

been reported in patients treated with leflunomide. Some cases were serious and some had a fatal outcome. Patients taking leflunomide and presenting with unexplained chronic diarrhoea or weight loss, should be investigated for colitis.

Hematologic

Monitoring for hematologic toxicity must be adhered to (see 7 Warnings and Precautions, Monitoring and Laboratory Tests).

APO-LEFLUNOMIDE is contraindicated in patients with impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid arthritis (see 2 Contraindications). In patients with a lesser degree of pre-existing anemia, leucopenia, and/or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk of hematological disorders is increased. The same effects also occur in patients on concomitant myelosuppresive medications, for example methotrexate, therefore strict vigilance in monitoring is recommended for all patients on leflunomide on concomitant myelosuppressive medication. If such effects occur, a washout procedure to reduce plasma levels of A771726 should be considered.

In case of severe hematological reactions, including pancytopenia, APO-LEFLUNOMIDE and any concomitant myelosuppressive medication must be discontinued and a washout procedure initiated (see 7 Warnings and Precautions, General, Washout Procedures).

Hepatic/Biliary/Pancreatic

Monitoring for hepatotoxicity must be adhered to (see 7 Warnings and Precautions, Monitoring and Laboratory Tests).

APO-LEFLUNOMIDE is contraindicated in patients with impairment of liver function (see 2 Contraindications). Given the possible risk of increased hepatotoxicity and the role of the liver in drug activation, elimination and recycling, the use of APO-LEFLUNOMIDE is not recommended in patients with positive Hepatitis B or C serologies or pre-existing hepatic disease.

Rare cases (defined by Regulatory definition as events occurring at a frequency ranging from 0.01 to 0.1%) of serious liver injury, including liver failure some with a fatal outcome, have been reported during treatment with leflunomide. Most of the cases occurred within the first 6 months of treatment. While confounding factors were seen in many cases such as other hepatotoxic drugs such as methotrexate and/or nonsteroidal anti-inflammatory drugs (NSAIDs), a causal relationship to leflunomide cannot be excluded. It is essential that the monitoring recommendations be adhered to and washout procedure performed in appropriate cases (see 7 Warnings and Precautions, Monitoring and Laboratory Tests).

Due to a potential for additive hepatotoxic effects, it is recommended that alcohol consumption be avoided during treatment with leflunomide.

In clinical trials, leflunomide treatment was associated with elevations of liver function tests, primarily ALT (SGPT) and AST (SGOT) in a significant number of patients; these effects were generally reversible. Most transaminase elevations were mild (≤ 2xULN) (upper limit of normal) and usually resolved while continuing treatment. Clinically significant elevations (> 2 and ≤ 3x ULN) were less common and were generally asymptomatic and reversible with dose reduction or, if persistent, by discontinuing leflunomide. More marked elevations (> 3xULN) occurred infrequently and resolved after discontinuation of leflunomide. Some patients received cholestyramine to enhance clearance. Overall, persistent elevations after dose reduction were uncommon and were usually associated with concomitant NSAIDs use. Limited biopsy data did not suggest that leflunomide was associated with the development of cirrhosis or hepatic fibrosis.

The following table shows liver enzyme elevations seen with monthly monitoring in clinical trials US301, MN301 and MN302. It was notable that the absence of folate use in MN302 was associated with a considerably greater incidence of liver enzyme elevation on methotrexate.

Table 2. Liver Enzyme Elevations > 3-fold Upper Limit of Normal (ULN)

	US301 no. of patients (% patients)			MN301 no. of patients (% patients)			MN302 no. of patients (% patients)	
	LEF	PBO	MTX	LEF	PBO	SSZ	LEF	MTX
ALT (SGPT) > 3-fold ULN	8	3	5	2	1	2	13	83
(%)	(4.4)	(2.5)	(2.7)	(1.5)	(1.1)	(1.5)	(2.6)	(16.7)
Reversed to ≤ 2-fold ULN	8	3	5	2	1	2	12	82
Timing of Elevation								
0-3 Months	6	1	1	2	1	2	7	27
4-6 Months	1	1	3	-	-	-	1	34
7-9 Months	1	1	1	-	-	-	-	16
10-12 Months	-	-	-	-	-	-	5	6
AST (SGOT) > 3-fold ULN	4	2	1	2	0	5	7	29
(%)	(2.2)	(1.7)	(0.6)	(1.5)		(3.6)	(1.4)	(5.8)
Reversed to ≤ 2-fold ULN	4	2	1	2		4	5	29
Timing of Elevation								
0-3 Months	2	1	-	2	-	4	3	10
4-6 Months	1	1	1	-	-	1	1	11
7-9 Months	1	-	-	-	-	-	-	8
10-12 Months	-	-	-	-	-	-	1	-

LEF=leflunomide, SSZ=sulfasalazine, PBO=placebo, MTX=methotrexate

Guidelines for dose adjustment or discontinuation based on the severity and persistence of ALT (SGPT) elevation are recommended as follows: If ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal persist or if ALT (SGPT) elevations of more than 3-fold the upper limit of normal are present, leflunomide should be discontinued. Cholestyramine or activated charcoal should be administered to more rapidly lower A771726 level (see 7 Warnings and Precautions, General, Washout Procedures and Monitoring and Laboratory Tests).

Rare elevations of alkaline phosphatase and bilirubin have been observed. Trial US301 used ACR

Methotrexate Liver Biopsy Guidelines for monitoring therapy. One of 182 patients receiving leflunomide and 1 of 182 patients receiving methotrexate underwent liver biopsy at 106 and 50 weeks, respectively. The biopsy for the leflunomide subject was Roegnik Grade IIIA and for the methotrexate subject Roegnik Grade I.

Immune

APO-LEFLUNOMIDE is not recommended for patients with bone marrow dysplasia, or severe, uncontrolled infections or immuno-deficiency due to causes other than rheumatoid arthritis (see 2 Contraindications).

Medications like APO-LEFLUNOMIDE that have immunosuppression potential may cause patients to be more susceptible to infections, including opportunistic infections (see 8.2 Clinical Trial Adverse Reactions). Infections may be more severe in nature.

It is known that patients with rheumatoid arthritis have an increased risk of severe infections, which may lead to sepsis and death. Rare cases of severe infection (including *Pneumocystis jiroveci* and cytomegalovirus infections) and sepsis (with fatal outcome in isolated cases) were reported in patients treated with leflunomide. Although in most cases a causal relationship to leflunomide has not been established and multiple confounding factors were present, infections developing in patients receiving APO-LEFLUNOMIDE may require early and vigorous treatment.

In the event that a severe or uncontrolled infection occurs, it may be necessary to interrupt APO-LEFLUNOMIDE treatment and administer a washout procedure (see 7 Warnings and Precautions, General, Washout Procedures).

Leflunomide has not been studied in patients with a positive tuberculosis screen, and the safety of leflunomide in individuals with latent tuberculosis infection is unknown. Before starting treatment, all patients should be evaluated for active and inactive ("latent") tuberculosis. Patients testing positive in tuberculosis screening should be treated by standard medical practice prior to therapy with leflunomide. Patients with a history of tuberculosis should be carefully monitored because of the possibility of reactivation of the infection.

Monitoring and Laboratory Tests

APO-LEFLUNOMIDE should be administered to patients only under careful medical supervision.

AST (SGOT) and ALT (SGPT) must be checked before initiation of the treatment and at monthly or more frequent intervals during the first 6 months, and every 8 weeks thereafter (See 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic).

ALT (SGPT) values are elevated more frequently than AST (SGOT).

For confirmed ALT (SGPT) elevations between 2- and 3-times the upper limit of normal, dose may be reduced from 20 to 10 mg/day and monitoring should be performed weekly. If ALT (SGPT) elevations of more than 2-times the upper limit of normal persist, or, if confirmed ALT (SGPT) increases to more than 3-times the upper limit of normal, APO-LEFLUNOMIDE must be discontinued and washout procedures initiated.

If a severe undesirable effect of APO-LEFLUNOMIDE occurs, or if for any other reason the active metabolite needs to be cleared rapidly from the body (e.g.: desired or unintended pregnancy, switching to another DMARD such as methotrexate), the washout procedures should be initiated. Cholestyramine or activated charcoal should be administered to more rapidly lower A771726 levels (see 2 Contraindications, 7 Warnings and Precautions, General, Washout Procedures).

A complete blood cell count, including differential white blood cell count and platelets, must be performed before start of APO-LEFLUNOMIDE treatment as well as every 2 weeks for the first 6 months of treatment and every 8 weeks thereafter (see 7 Warnings and Precautions, Hematologic).

Blood pressure must be checked before the start of APO-LEFLUNOMIDE treatment and periodically thereafter (see 7 Warnings and Precautions, Cardiovascular and 8.2 Clinical Trial Adverse Reactions).

In patients with a current or previous history of pulmonary disease or who have been recently treated with drugs known to induce interstitial lung disease, it is recommended that pulmonary status be evaluated prior to initiation of APO-LEFLUNOMIDE therapy and that patients be closely monitored during treatment. Before starting treatment, all patients should be evaluated for active and inactive ("latent") tuberculosis. Patients with a history of tuberculosis should be carefully monitored because of the possibility of reactivation of the infection.

Other Laboratory Tests Changes:

Due to an uricosuric effect presumably at the brush border of the proximal renal tubule, uric acid levels usually decrease. Phosphaturia and hypokalemia may also occur.

Musculoskeletal

Myopathy and/or muscle injury including rhabdomyolysis, myositis, polymyositis, dermatomyositis, and immune-mediated necrotizing myopathy have been reported with leflunomide treatment. Follow-up with patients periodically for muscle pain and weakness. Monitor the patients for elevation of CK levels as necessary. If a patient taking APO-LEFLUNOMIDE develops myopathy and/or muscle injury, consider discontinuing APO-LEFLUNOMIDE, and performing a washout procedure (see 7 Warnings and Precautions, General, Washout Procedures).

Neurologic

Peripheral Neuropathy

Cases of peripheral neuropathy have been reported in patients receiving leflunomide. Most patients recovered after discontinuation of leflunomide, but some patients had persistent symptoms. Age older than 60 years, concomitant neurotoxic medications, and diabetes may increase the risk for peripheral neuropathy. If a patient taking APO-LEFLUNOMIDE develops a peripheral neuropathy, consider discontinuing APO-LEFLUNOMIDE and performing a washout procedure (see 7 Warnings and Precautions, General, Washout Procedures).

Perioperative Considerations

Impaired wound-healing after surgery can occur in patients during therapy with APO-LEFLUNOMIDE. Based on an individual assessment, interruption of leflunomide treatment in the peri-surgical period should be considered, administering a washout procedure. In case of interruption, the decision to resume leflunomide should be based on clinical judgment of adequate wound healing (see 7 Warnings and Precautions, General, Washout Procedures and 7 Warnings and Precautions, Skin).

Renal

APO-LEFLUNOMIDE is contraindicated in patients with moderate to severe renal impairment. Because the kidney plays a role in the elimination of leflunomide, and without sufficient studies of the use of leflunomide in patients with renal insufficiency, caution should be used when considering the administration of APO-LEFLUNOMIDE to patients with mild renal insufficiency.

Reproductive Health

- **Fertility**

  Leflunomide had no effect on fertility in either male or female rats at oral doses up to 0.4 mg/kg (approximately 1/30 the human A771726 exposure based on AUC).

- **Teratogenic Risk**

  Pregnancy must be avoided if either partner is receiving APO-LEFLUNOMIDE.

  Females

  There are no adequate and well-controlled studies evaluating leflunomide in pregnant women. However, based on animal studies, leflunomide may cause fetal death or teratogenic effects when administered to a pregnant woman. Women of childbearing potential must not be started on APO-LEFLUNOMIDE until pregnancy is excluded and it has been confirmed that they are using reliable contraception.

Before starting treatment with APO-LEFLUNOMIDE, patients must be fully counseled on the potential for serious risk to the fetus. Patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing. Should pregnancy occur, the physician and patient should discuss the risk of continuing the pregnancy (see 2 Contraindications and 7.1.1 Pregnancy). It is possible that rapidly lowering the blood level of the active metabolite, by instituting the drug elimination procedure described below, at the first delay of menses may decrease the risk to the fetus from APO-LEFLUNOMIDE.

For women who have received APO-LEFLUNOMIDE treatment and wish to become pregnant, one of the following procedures is recommended:

- After stopping treatment with APO-LEFLUNOMIDE, cholestyramine 8 g is administered 3 times daily for a period of 11 days OR

- After stopping treatment with APO-LEFLUNOMIDE, 50 g of activated charcoal is administered 4 times daily for a period of 11 days.

The plasma levels of the active metabolite (A771726) must be less than 0.02 mg/L (0.02 mcg/mL). Below this plasma level (to be verified by 2 separate tests at an interval of at least 14 days), the teratogenic risk is considered very low (see 2 Contraindications and 7 Warnings and Precautions, General, Washout Procedures).

Without the drug elimination procedure, it may take up to 2 years to reach A771726 levels < 0.02 mg/L. However, also after a such waiting period, verification of A771726 levels less than 0.02 mg/L (0.02 mcg/mL) by 2 separate tests at an interval of a least 14 days is required.

If a waiting period of up to approximately 2 years under reliable contraception is considered unpractical, prophylactic institution of a washout procedure may be advisable. (see 7 Warnings and Precautions, General, Washout Procedures)

Reliable contraception with oral contraceptive may not be guaranteed during the washout procedure with cholestyramine or activated charcoal. Use of alternative contraceptive methods is recommended.

Males

APO-LEFLUNOMIDE must not be used by men who could potentially father a child and are not using reliable contraception during and for a total of 2 years after treatment with APO-LEFLUNOMIDE, if no elimination procedure is used.

There are no specific data on the risk of male-mediated foetal toxicity. However, animal studies to evaluate this specific risk have not been conducted. To minimise any possible

risk, men wishing to father a child should consider discontinuing use of APO-LEFLUNOMIDE and use elimination procedure or wait 2 years after treatment cessation.

For men having received APO-LEFLUNOMIDE treatment and wishing to father a child, plasma levels of the active metabolite (A771726) must be less than 0.02 mg/L (0.02 mcg/mL) to be verified by two separate tests at an interval of at least 14 days. After the second test confirming that the plasma concentration is below 0.02 mg/L an additional waiting period of 3 months is required. After that period, the risk of male-mediated foetal toxicity is considered very low (see 2 Contraindications and 7 Warnings and Precautions, General, Washout Procedures).

Respiratory

Rare (< 0.1%) spontaneous reports of interstitial lung disease occurring during treatment with leflunomide have been received worldwide (see 8.3 Less Common Clinical Trial Adverse Reactions, Respiratory, Thoracic and Mediastinal Disorders). Several of these cases had a fatal outcome. A large-scale cohort study to assess the risk of Interstitial lung disease (ILD) associated with leflunomide use was sponsored by Sanofi-Aventis and the Canadian Institutes of Health Research. The study used linked databases, prescribing and administrative information, for more than 235,000 patients with rheumatoid arthritis (RA). It was found that the risk of ILD was increased in patients with a history of methotrexate (MTX) use or interstitial lung disease (RR=2.6 [95% CI: 1.2 to 5.6]).

In a Japanese postmarketing surveillance program of 3658 patients with rheumatoid arthritis, the rate of interstitial lung disease was estimated at 0.8%, regardless of causality. Twenty-nine (29) cases of interstitial pneumonitis were reported, 11 with a fatal outcome. Assessment of the causality between leflunomide use and the reported interstitial lung disease is frequently confounded by pre-existing pulmonary disease (e.g. interstitial pneumonitis), and/or previous or concomitant use of other DMARDs known to induce interstitial lung disease (including methotrexate).

In patients with a current or previous history of pulmonary disease or who have been recently treated with drugs known to induce interstitial lung disease, it is recommended that pulmonary status be evaluated prior to initiation of APO-LEFLUNOMIDE therapy and that patients be closely monitored during treatment.

Interstitial lung disease is a potentially fatal disorder, which 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 the therapy and for further investigation, as appropriate. If discontinuation of the drug is needed, the long half-life of the active metabolite of APO-LEFLUNOMIDE may necessitate the initiation of wash-out procedures (see 7 Warnings and Precautions, General, Washout Procedures).

Patients should be informed about the early warning signs of interstitial lung disease and asked to

contact their physician as soon as possible if these symptoms appear or worsen during therapy.

Skin

In case of ulcerative stomatitis, APO-LEFLUNOMIDE administration should be discontinued.

Cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients treated with leflunomide. As soon as skin and/or mucosal reactions are observed which raise the suspicion of such severe reactions, APO-LEFLUNOMIDE and any other possibly associated medication must be discontinued, and a washout procedure initiated immediately. A complete washout is essential in such cases. In such cases re-exposure to APO-LEFLUNOMIDE is contraindicated (see 2 Contraindications and 7 Warnings and Precautions, General, Washout Procedures).

Hemophagocytic lymphohistiocytosis (HLH) / Macrophage activation syndrome (MAS):

HLH including MAS is a serious and potentially life-threatening hyperinflammatory condition. Cases of DRESS can be complicated by HLH, including MAS. The co-occurrence of DRESS and HLH/MAS is rare, severe, and life-threatening. HLH/MAS cases have also been reported independently of DRESS. If patients develop any of these conditions, stop APO-LEFLUNOMIDE treatment and perform an accelerated drug elimination procedure (see 7 Warnings and Precautions, General, Washout Procedures). Early recognition and prompt management is important to improve outcomes.

Skin ulcers can occur in patients during therapy with APO-LEFLUNOMIDE. If APO-LEFLUNOMIDE - associated skin ulcer is suspected or if skin ulcers persist despite appropriate therapy, APO-LEFLUNOMIDE discontinuation and a complete washout procedure should be considered. The decision to resume APO-LEFLUNOMIDE following skin ulcers should be based on clinical judgment of adequate wound healing.

Impaired wound-healing after surgery can occur in patients during therapy with APO-LEFLUNOMIDE. (see 7 Warnings and Precautions, Perioperative Considerations and General, Washout Procedures).

7.1 Special Populations

7.1.1 Pregnancy

APO-LEFLUNOMIDE is contraindicated for pregnant women or women of child bearing potential. APO-LEFLUNOMIDE is contraindicated for male subjects who wish to father a child (see 2 Contraindications and 7 Warnings and Precautions, Reproductive Health).

7.1.2 Breastfeeding

Animal studies indicate that leflunomide or its metabolites pass into breast milk. Therefore, APO-

LEFLUNOMIDE is contraindicated for nursing mothers (see 2 Contraindications).

7.1.3 Pediatrics

The safety and efficacy of leflunomide in the pediatric population have not been fully evaluated, and its use in patients less than 18 years of age is contraindicated.

7.1.4 Geriatrics

No dosage adjustment is needed in patients over 65 years of age.

8 Adverse Reactions

8.1 Adverse Reaction Overview

Hypertension, gastrointestinal disturbances, weight loss, headache, dizziness, paresthesia, asthenia, musculoskeletal and skin disorder are considered as some common adverse reactions seen with leflunomide**.**

Leucopenia and hypersensitivity reactions may occur and cases of Stevens-Johnson syndrome or toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported.

Hepatotoxicity has occurred. It is usually mild and reversible but cases of severe, sometimes fatal, liver disease, including acute hepatic necrosis, have been observed. There have been reports of pancreatitis, interstitial lung disease, and infections, including fatal sepsis. (See 8.3 Less Common Clinical Trial Adverse Reactions and 8.5 Post-Market Adverse Reactions)

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

There were a total of 5419 adverse events reported in 1339 subjects treated with leflunomide. Four percent (4%) of the subjects in controlled studies of leflunomide had a dose reduction as a result of an adverse event and 15.5% discontinued study treatment due to adverse events. There was a total of 377 serious adverse events which occurred in 294 (22%) leflunomide treated subjects. The percent of leflunomide treated patients experiencing an adverse event was similar to methotrexate, the next largest treatment population.

The most common adverse events, in the controlled clinical trials, considered related to leflunomide administration were of gastrointestinal origin and consisted predominantly of diarrhea (26.7% leflunomide, 11.9% placebo, 9.8% sulfasalazine, 12.5% methotrexate), LFT (liver function test) abnormalities (10.2% leflunomide, 2.4% placebo, 3.8% sulfasalazine, 15.1%

methotrexate), abdominal pain (5.7% leflunomide, 4.3% placebo, 6.8% sulfasalazine, 7.5% methotrexate), and nausea and/or vomiting (17.8% leflunomide, 14.3% placebo, 22.6% sulfasalazine, 19.9% methotrexate). These disorders may as well be associated with concomitant NSAID administration, common in all treatment groups. The occurrences of hypertension and hypokalemia observed in patients treated with leflunomide may have been influenced by concomitant NSAID and/or steroid use. Monitoring blood pressure in patients on leflunomide should be considered as addition to the recommended Monitoring of hematologic and hepatic function. (See 7 Warnings and Precautions, Monitoring and Laboratory Tests)

Adverse reactions associated with the use of leflunomide in rheumatoid arthritis include diarrhea, elevated liver transaminases (ALT [SGPT] and AST [SGOT]), alopecia, rash, and hypertension. In the controlled studies, the following adverse events were reported regardless of causality:

Table 3. Percentage of Patients with Adverse Events ≥ 3% in any Leflunomide Treated Group

	All RA Studies	Placebo-Controlled Trials				Active-Controlled Trials	
		MN 301 and US 301				MN 302[†]	
	LEF (N=1339)	LEF (N=315)	PBO (N=210)	SSZ (N=133)	MTX (N=182)	LEF (N=501)	MTX (N=498)
GENERAL DISORDER							
Allergic Reaction	2%	5%	2%	0%	6%	1%	2%
Worsening RA	8%	5%	11%	20%	4%	17%	19%
Asthenia	3%	6%	4%	5%	6%	3%	3%
Flu Syndrome	2%	4%	2%	0%	7%	0%	0%
Infection	4%	0%	0%	0%	0%	0%	0%
Injury Accident	5%	7%	5%	3%	11%	6%	7%
Pain	2%	4%	2%	2%	5%	1%	< 1%
Abdominal Pain	6%	5%	4%	4%	8%	6%	4%
Back Pain	5%	6%	3%	4%	9%	8%	7%
CARDIOVASCULAR DISORDERS							
Hypertension	10%	9%	4%	4%	3%	10%	4%
Chest Pain	2%	4%	2%	2%	4%	1%	2%
GASTROINTESTINAL DISORDERS							
Anorexia	3%	3%	2%	5%	2%	3%	3%
Diarrhea	17%	27%	12%	10%	20%	22%	10%
Dyspepsia	5%	10%	10%	9%	13%	6%	7%
Gastroenteritis	3%	1%	1%	0%	6%	3%	3%
Abnormal Liver Function Tests	5%	10%	2%	4%	10%	6%	17%
Nausea	9%	13%	11%	19%	18%	13%	18%
GI/Abdominal Pain	5%	6%	4%	7%	8%	8%	8%
Mouth Ulcer	3%	5%	4%	3%	10%	3%	6%
Vomiting	3%	5%	4%	4%	3%	3%	3%
BLOOD AND LYMPHATIC DISORDERS							

	All RA Studies	Placebo-Controlled Trials				Active-Controlled Trials	
		MN 301 and US 301				MN 302†	
	LEF (N=1339)	LEF (N=315)	PBO (N=210)	SSZ (N=133)	MTX (N=182)	LEF (N=501)	MTX (N=498)
Leucopenia (> 2 G/L)	3%	-	0%	2%	1%	4%	3%
METAB. & NUTRITION DISORDERS							
Hypokalemia	1%	3%	1%	1%	1%	1%	<1%
Weight Decrease	4%	2%	1%	2%	0%	2%	2%
MUSCULOSKELETAL SYSTEM and CONNECTIVE TISSUE DISORDERS							
Leg Cramps	1%	4%	2%	2%	6%	0%	0%
Joint Disorder	4%	2%	2%	2%	2%	8%	6%
Synovitis	2%	< 1%	1%	0%	2%	4%	2%
Tendosynovitis	3%	2%	0%	1%	2%	5%	1%
NERVOUS SYSTEM DISORDERS							
Dizziness	4%	5%	3%	6%	5%	7%	6%
Headache	7%	13%	11%	12%	21%	10%	8%
Paresthesia	2%	3%	1%	1%	2%	4%	3%
RESPIRATORY, THORACIC and MEDIASTINAL DISORDERS							
Bronchitis	7%	5%	2%	4%	7%	8%	7%
Increased Cough	3%	4%	5%	3%	6%	5%	7%
Respiratory Infection	15%	21%	21%	20%	32%	27%	25%
Pharyngitis	3%	2%	1%	2%	1%	3%	3%
Pneumonia	2%	3%	0%	0%	1%	2%	2%
Rhinitis	2%	5%	2%	4%	3%	2%	2%
Sinusitis	2%	5%	5%	0%	10%	1%	1%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS							
Alopecia	10%	9%	1%	6%	6%	17%	10%
Eczema	2%	1%	1%	1%	1%	3%	2%
Pruritis	4%	5%	2%	3%	2%	6%	2%
Rash	10%	12%	7%	11%	9%	11%	10%
Dry Skin	2%	3%	2%	2%	0%	3%	1%
RENAL AND URINARY DISORDERS							
Urinary Tract Infection	5%	5%	7%	4%	2%	5%	6%

† Study MN 302, an active-controlled study, treated a total of 999 subjects using 1:1 randomization to (1) Leflunomide 20 mg/day after a loading dose of 100 mg/day for 3 days, or (2) methotrexate 10 mg/week or escalation to 15 mg/week. Treatment duration was 52 weeks.

LEF = leflunomide, SSZ= sulfasalazine, PBO= placebo, MTX= methotrexate, RA=Rheumatoid Arthritis

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse events have been reported in 1% to < 3%, less than 1%, less than 0.1% or less than 0.01% of the rheumatoid arthritis patients in the leflunomide treatment group in controlled clinical trials or during post-marketing surveillance:

Blood and Lymphatic System Disorders:
1% to < 3%: anemia (including iron deficiency anemia), ecchymosis, leucopenia (leucocytes > $2X10^9$/l [2 G/L]).
Less than 1%: eosinophilia, leucopenia (leucocytes < 2G /L), lymphadenopathy.

Cardiovascular Disorders:
1% to < 3%: angina pectoris, palpitation, tachycardia, vasodilatation, varicose vein.

Endocrine Disorders
1% to < 3%: diabetes mellitus, hyperthyroidism.

Eye Disorders:
1% to < 3%: amblyopia, cataract, conjunctivitis, eye disorders.

Gastrointestinal Disorders:
1% to < 3%: colitis, constipation, esophagitis, flatulence, gastritis, gingivitis, melena, oral moniliasis, pharyngitis, salivary gland enlarged, stomatitis (or aphthous stomatitis), tooth disorder, taste perversion.

General Disorders:
1% to < 3%: abscess, cyst, fever, hernia, malaise, pain, neck pain, pelvic pain, migraine.

The risk of malignancy, particularly lymphoproliferative disorders, is also known to be increased with use of some immunosuppressive drugs. (See 7 Warnings and Precautions, Carcinogenesis and Genotoxicity).

Hepatobiliary Disorders:
1% to < 3%: cholelithiasis
Severe disturbances in liver function; increase in alkaline phosphatase, bilirubin, less often gamma-GT and lactate dehydrogenase (LDH).

Metabolism and nutrition disorders:
1% to < 3%: creatine phosphokinase increased, peripheral edema, hyperglycemia, hyperlipidemia
Less than 1%: hypokalemia, hypophosphatemia.

Uric acid level usually decreases, due to an uricosuric effect.

Musculoskeletal System and Connective Tissue Disorders:
1% to < 3%: arthrosis, bursitis, muscle cramps, myalgia, bone necrosis, bone pain, tendon rupture.

Nervous System Disorders:
1% to < 3%: anxiety, asthenia, depression, dry mouth, insomnia, neuralgia, neuritis, sleep disorder, sweating, vertigo.

Respiratory, Thoracic and Mediastinal Disorders:
1% to < 3%: asthma, dyspnea, epistaxis, lung disorder

Skin and Subcutaneous Tissue Disorders and Allergic Reactions:
1% to < 3%: acne, contact dermatitis, fungal dermatitis, hair discoloration, hematoma, herpes simplex, herpes zoster, nail disorder, skin nodule, subcutaneous nodule, maculopapular rash, skin disorder, skin discolouration, skin ulcer Less than 1%: urticaria, anaphylactoid reactions, severe anaphylactic reaction

Renal and Urinary Disorders:
1% to < 3%: albuminuria, cystitis, dysuria, hematuria, prostate disorder, urinary frequency

Reproductive System and Breast Disorders:
1% to < 3%: menstrual disorder, vaginal moniliasis

Causal relationship of these events to leflunomide has not been established

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.

8.5 Post-Market Adverse Reactions

Blood and Lymphatic System Disorders:
Leucopenia, pancytopenia, thrombocytopenia, agranulocytosis.

Cardiovascular system:
Pulmonary hypertension (see 7 Warnings and Precautions, Cardiovascular).

Gastrointestinal system:
Colitis including ulcerative, microscopic colitis (lymphocytic, and collagenous colitis) and Crohn's Disease (see 7 Warnings and Precautions, Gastrointestinal).

Hepatobiliary Disorders:
Hepatitis, jaundice/ cholestasis, severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal, pancreatitis.

Hypersensitivity:
Angioedema.

Infection and Infestations:

Severe infections including opportunistic infections and sepsis, which may be fatal.

Nervous System Disorders:
Peripheral neuropathy.

Respiratory, Thoracic and Mediastinal Disorders:
Interstitial lung disease (including interstitial pneumonitis and pulmonary fibrosis), sometimes fatal and pulmonary nodules (in rare instances, may result in recurrent pneumothorax).

Skin and Subcutaneous Tissue Disorders and Allergic Reactions:
Cutaneous lupus erythematosus, erythema multiforme, impaired wound healing, pustular psoriasis or worsening psoriasis, Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis, including cutaneous necrotizing vasculitis, drug reaction with eosinophilia and systemic symptoms (DRESS) and skin ulcer.

9 Drug Interactions

9.2 Drug Interactions Overview

Increased side effects may occur when APO-LEFLUNOMIDE is given concomitantly with hepatotoxic, hematotoxic or immunosuppressive substances. This is also to be considered when APO-LEFLUNOMIDE treatment is followed by such drugs without a washout period (see 2 Contraindications and 7 Warnings and Precautions, General, Washout Procedures). Strict vigilance in monitoring of hepatic and hematologic functions is recommended for all patients prescribed APO-LEFLUNOMIDE with other medications associated with increased risk of hepatotoxicity or hematotoxicity.

Due to a potential for additive hepatotoxic effects, it is recommended that alcohol consumption be avoided during treatment with APO-LEFLUNOMIDE.

In vitro inhibition studies in human liver microsomes suggest that cytochrome P450 (CYP) 1A2, 2C19 and 3A4 are involved in leflunomide metabolism.

Following oral administration, APO-LEFLUNOMIDE is rapidly converted to the active metabolite, A771726. *In vitro* studies indicate that A771726 inhibits cytochrome P4502C9 (CYP2C9) activity.

Pharmacokinetic and pharmacodynamic interaction studies were conducted with A771726. As similar drug-drug interactions cannot be excluded for APO-LEFLUNOMIDE at recommended doses, the corresponding study results and recommendations should be considered in patients treated with APO-LEFLUNOMIDE.

In clinical trials no safety problems were observed when leflunomide and NSAIDs metabolised by CYP2C9 were co-administered. Caution is advised when leflunomide is given together with drugs, other than NSAIDs, that are metabolised by CYP2C9 such as phenytoin, warfarin, and tolbutamide. (See 9.4 Drug-Drug Interactions section)

9.4 Drug-Drug Interactions

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Aspirin, NSAIDs, Corticosteroids	T	No apparent interactions between leflunomide and concomitantly administered aspirin (acetylsalicylic acid), NSAIDs, and/or low dose corticosteroids.	In clinical trials of over 1339 rheumatoid arthritis patients there were no apparent interactions between leflunomide and concomitantly administered aspirin (acetylsalicylic acid), NSAIDs, and/or low dose corticosteroids. It has been shown that corticosteroid doses may be reduced gradually in patients who respond to leflunomide. *In vitro* studies indicate that A771726 inhibits cytochrome P4502C9 (CYP2C9) activity. In clinical trials no safety problems were observed when leflunomide and NSAIDs metabolised by CYP2C9 were co-administered. Based on protein binding measured *in vitro* using therapeutic concentrations, there was no effect of ibuprofen, or diclofenac on the protein binding of A771726. A771726 lead to a 13% to 50% increase in the unbound fractions of diclofenac and ibuprofen, which would not be expected to be clinically significant. Aspirin (acetylsalicylic acid), NSAIDs, and/or low dose corticosteroids may be continued during treatment with leflunomide. These combined used of leflunomide with NSAIDS and/or corticosteroids may be associated with hypertension.
Caffeine (CYP1A2 substrate	C	Repeated doses of A771726 decreased mean C_{max} and AUC of caffeine (CYP1A2 substrate) by 18% and 55%, respectively, suggesting that A771726 may be a weak inducer of CYP1A2 *in vivo*	Therefore, medicinal products metabolised by CYP1A2 (such as duloxetine, theophylline and tizanidine) should be used with caution during concomitant treatment, as it could lead to the reduction of the efficacy of these products. Clinical data with leflunomide are not available.
Cholestryramine or activated charcoal	T	Decrease in plasma A771726	Concomitant administration of leflunomide with cholestyramine or

Proper/ Common name	Source of Evidence	Effect	Clinical comment
			activated charcoal will lead to a rapid and significant decrease in plasma A771726 (the active metabolite of leflunomide) concentration. The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of A771726.
BCRP substrates	C & CT	No pharmacokinetic interaction between leflunomide and methotrexate was noted. Repeated doses of A771726 increased mean rosuvastatin C_{max} and AUC (2.65- and 2.51-fold, respectively) (see below)	Although a pharmacokinetic interaction with a BCRP substrate (rosuvastatin) was observed with A771726 (see below), no pharmacokinetic interaction between leflunomide (10 to 20 mg per day) and methotrexate (a BCRP substrate; 10 to 25 mg per week) was demonstrated in a study involving 12 patients.
BCRP and /or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates	C	Repeated doses of A771726 increased mean rosuvastatin C_{max} and AUC by 2.65- and 2.51-fold, respectively, without any apparent impact on the HMG-CoA reductase activity.	If used together with leflunomide, the dose of rosuvastatin should be reduced by 50% and should not exceed 10 mg once daily. For other substrates of BCRP (e.g., methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-CoA reductase inhibitors (e.g., simvastatin, atorvastatin, pravastatin) methotrexate, nateglinide, repaglinide, rifampin concomitant administration should also be undertaken with caution. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered. Clinical data with leflunomide are not available.
Cimetidine	T	No changes in the pharmacokinetics of A771726 or TFMA	When co-administered with cimetidine (nonspecific weak Cytochrome P450 inhibitor), there were no changes in the pharmacokinetics of A771726 or TFMA, and slight increases in leflunomide concentrations were observed in some subjects.

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Methotrexate	CT	No pharmacokinetic interaction between the methotrexate and leflunomide was noted. Risk of additive toxicity (i.e., hepatotoxicity).	Concomitant administration of leflunomide with methotrexate has not been approved in Canada. In an open label study, 30 patients with active rheumatoid arthritis despite methotrexate therapy (17±4 mg/week (mean±S.D.) for at least six months were administered leflunomide 10-20 mg/day. Twenty-three patients completed one year of treatment. No pharmacokinetic interaction between the methotrexate and leflunomide was noted. A 2- to 3-fold elevation in liver enzymes was seen in 5 of 30 patients. All elevations resolved, 2 with continuation of both drugs and 3 after discontinuation of leflunomide. A more than 3-fold increase was seen in another 5 patients. All of these also resolved, 2 with continuation of both drugs and 3 after discontinuation of leflunomide. Sixteen patients met ACR 20% criteria for clinical response. In the two patients that underwent liver biopsies there was no evidence of significant fibrosis. Changing from leflunomide to methotrexate without a washout period may raise the possibility of additive risks even for a long time after the switching (i.e., kinetic interaction, organ toxicity) (see 7 Warnings and Precautions, General). In addition, if leflunomide and methotrexate are given concomitantly, ACR guidelines for monitoring methotrexate liver toxicity must be followed with ALT (SGPT), AST (SGOT), and serum albumin testing monthly (See 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic).
Other DMARDs	T	Risk of additive or synergistic toxicity (e.g., hepato- or hematotoxicity)	The combined use of leflunomide with antimalarials, intramuscular or oral gold, D penicillamine or azathioprine has not been adequately studied. The risk associated with combination therapy, in particular in long-term treatment, is unknown. Since such therapy can lead to additive or even

Proper/ Common name	Source of Evidence	Effect	Clinical comment
			synergistic toxicity (e.g. hepato- or hematotoxicity), combination with another DMARD is not advisable.
Warfarin	C	Repeated doses of A771726 had no effect on the pharmacokinetics of S-warfarin suggesting that A771726 is not an inhibitor or an inducer of CYP2C9.	Based on protein binding measured *in vitro* using therapeutic concentrations, there was no effect of warfarin on the protein binding of A771726. A771726 had no effect on the binding of warfarin. A pharmacodynamic interaction with warfarin was observed with A771726 in a clinical pharmacology study. Repeated doses of A771726 had no effect on the pharmacokinetics of S-warfarin suggesting that A771726 is not an inhibitor or an inducer of CYP2C9. The treatment ratio estimates of A771726+ warfarin vs. warfarin alone were as follows: C_{max}: 1.08 (90%CI: 1.00, 1.16) and AUC: 1.12 (90%CI: 1.08, 1.15). However, a 25% decrease in peak international normalised ratio (INR) was observed when A771726 was coadministered with warfarin as compared with warfarin alone. Clinical data with leflunomide are not available. There have been case reports of increased prothrombin time when leflunomide and warfarin were co-administered. When warfarin is co-administered, caution is advised and close INR follow-up and monitoring is recommended.
Tolbutamide and Phenytoin	T	*In vitro*, A771726 lead to a 13% to 50% increase in the unbound fractions of tolbutamide, which would not be expected to be clinically significant.	*In vitro* studies indicate that A771726 inhibits cytochrome P4502C9 (CYP2C9) activity. Caution is advised when leflunomide is given together with drugs, other than NSAIDs that are metabolised by CYP2C9 such as tolbutamide and phenytoin. *In vitro*, A771726 lead to a 13% to 50% increase in the unbound fractions of tolbutamide, which would not be expected to be clinically significant. Tolbutamide led to an increase in the percent of unbound A771726, which was

Proper/ Common name	Source of Evidence	Effect	Clinical comment
			dependent upon the concentration of tolbutamide but independent of the concentration of A771726.
Oral contraceptives	T	Increase in mean ethinylestradiol C_{max} and AUC_{0-24} and levonorgestrel C_{max} and AUC_{0-24} following repeated doses of A771726	In a study in which leflunomide was given concomitantly with a triphasic oral contraceptive pill containing 30 mcg ethinylestradiol to healthy female volunteers, there was no reduction in contraceptive activity and A771726 pharmacokinetic parameters were within predicted ranges. A pharmacokinetic interaction with oral contraceptives (0.03 mg ethinylestradiol and 0.15 mg levonorgestrel) was observed with A771726. There was an increase in mean ethinylestradiol C_{max} and AUC_{0-24} (1.58- and 1.54-fold, respectively) and levonorgestrel C_{max} and AUC_{0-24} (1.33- and 1.41-fold, respectively) following repeated doses of A771726. While this interaction is not expected to adversely impact the efficacy of oral contraceptives, consideration should be given to the type of oral contraceptive treatment.
Organic anion transporter 3 (OAT3) substrates:	T	increase in mean cefaclor C_{max} and AUC (1.43- and 1.54-fold, respectively	Following repeated doses of A771726, suggesting that A771726 is an inhibitor of OAT3 *in vivo*. Therefore, when coadministered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution is recommended. Clinical data with leflunomide are not available.
Rifampin	T	Increase in A771726 levels	Following concomitant administration of a single dose of leflunomide to subjects receiving multiple doses of rifampin, A771726 levels were increased approximately 40% over those seen when leflunomide was administered alone. Because of the potential for leflunomide levels to continue to increase with multiple dosing, caution should be used if patients are to be receiving both leflunomide and rifampin.
Vaccination	T	Vaccination with	No clinical data are available on the

Proper/ Common name	Source of Evidence	Effect	Clinical comment
		live vaccines is, however, not recommended.	efficacy and safety of vaccination during leflunomide treatment. Vaccination with live vaccines is, however, not recommended. A live vaccine should only be given after a period of at least 6 months has elapsed after stopping leflunomide.
Repaglinide (CYP2C8 substrate):	C	increase in mean repaglinide C_{max} and AUC (1.7-and 2.4-fold, respectively)	There was an increase in mean repaglinide C_{max} and AUC (1.7- and 2.4-fold, respectively), following repeated doses of A771726, suggesting that A771726 is an inhibitor of CYP2C8 *in vivo*. Therefore, monitoring patients with concomitant use of drugs metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, is recommended as they may have higher exposure. Dose reduction for drugs metabolized by CYP2C8 may need to be considered based on the monitoring. Clinical data with leflunomide are not available.

Legend: C = Case Study; CT = Clinical Trial; T: Theoretical

9.5 Drug-Food Interactions

Interactions with food products and beverages have not been established.

Alcohol consumption should be avoided during treatment with APO-LEFLUNOMIDE due to a potential for additive hepatotoxic effects.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

Leflunomide is an isoxazole immunomodulatory agent which inhibits *de novo* pyrimidine synthesis and has antiproliferative activity. Following oral administration, it is rapidly metabolized to

A771726, which is active *in vitro* and is presumed to be the active drug *in vivo*. Leflunomide has demonstrated prophylactic and therapeutic effects in animal models of autoimmune disease. In addition, leflunomide has exhibited antiinflammatory and weak analgesic and antipyretic activity. In a model of experimental septicemia, leflunomide did not alter the resistance of mice to bacterial pathogens.

In vitro, after mitogen stimulation, A771726 inhibits T-cell proliferation, DNA synthesis, and expression of certain cell surface and nuclear antigens directly involved in T-cell activation and proliferation. It inhibits antigen-stimulated proliferation of human peripheral blood mononuclear cells (PBMCs) and proliferation in transformed murine and human cell lines, in a dose-dependent fashion. The antiproliferative activity is reversed by the addition of uridine to the cell culture, indicating that A771726 acts at the level of the *de novo* pyrimidine biosynthesis. Leflunomide inhibition of GvHD *in vivo* is also reversed by feeding uridine, further indicating that A771726 acts at the level of the *de novo* pyrimidine biosynthesis pathway.

It has been demonstrated that A771726 binds to and is a potent inhibitor of dihydroorotate dehydrogenase (DHODH), an enzyme in the *de novo* pyrimidine synthesis pathway important for DNA synthesis. In the heterotopic cardiac transplant model, DHODH activity is decreased in lymphocytes infiltrating heart allograft tissue in leflunomide-treated animals. *In vitro*, incubation of PHA/IL 2 stimulated human peripheral T cells with A771726 triggered cell cycle arrest at the GI phase or, in those cells undergoing DNA synthesis, at S phase. Exogenous uridine reversed this effect, and no increase in apoptotic cell numbers was observed. Increased levels of the tumor suppressor protein p53 with subsequent expression of the cyclin-dependent kinase (CDK) inhibitor p21 appear to mediate this reversible cell cycle arrest.

In vitro incubation of A771726 with rat, mouse, and human DHODH demonstrated inhibition of enzyme activity at concentrations lower than those, which exert antiproliferative effects upon rapidly dividing cells (10 to 367 mM). Rat and mouse enzymes are more sensitive to the inhibitory effect of A771726 (IC_{50} 0.14 ± 0.08 and 16 ±11 mcM, respectively) than the human enzyme (IC_{50} 46 ± 6 mcM).

Together, these data suggest that, *in vivo* at concentrations achievable in patients, leflunomide inhibits *de novo* pyrimidine synthesis in activated lymphocytes and other rapidly dividing cell populations resulting in reversible cell cycle arrest.

The inhibition of tyrosine kinase activities has also been reported for both *in vitro* and *in vivo* situations. These effects are observed at A771726 concentrations much higher than those needed for DHODH inhibition and could be secondary to the effect on DHODH. In addition, leflunomide orally and A771726 *in vitro* have been demonstrated to modulate the cell adhesion process in rheumatoid arthritis patients.

10.3 Pharmacokinetics

The pharmacokinetics of leflunomide, based upon plasma concentrations of the active metabolite, A771726, have been studied in healthy subjects and in patients with rheumatoid arthritis.

Absorption

After oral administration of a 100 mg dose of ^{14}C-leflunomide to healthy volunteers, leflunomide was not detectable (< 25 ng/mL) in plasma over the plasma sampling period (0.5 hrs to 37 days). Plasma concentrations of total radioactivity and A771726 were superimposable, demonstrating extensive conversion to the active metabolite A771726 during the absorption process. The minor metabolite 4-trifluoromethylaniline (TFMA) has been detected in the plasma of animals and man, but at concentrations (ng/mL) much less than those of A771726 (mcg/mL). The slow but nearly complete recovery of radioactivity as metabolites indicated near complete absorption of leflunomide in man.

In a 24-week study in patients with rheumatoid arthritis, steady-state was reached between 7 and 8 weeks. Mean plasma A771726 concentrations 24 hours after a 100 mg loading dose (8.5 mcg/mL) were twice those after a 50 mg loading dose (4.0 mcg/mL). Pre-dose plasma concentrations after 24 weeks of dosing were linearly related to the maintenance dose (9, 18, and 63 mcg/mL after 5, 10 or 25 mg/day, respectively). The pharmacokinetics of A771726 are, therefore, linear over the range of loading and maintenance doses to be used clinically.

After single doses of leflunomide to healthy subjects, peak plasma concentrations of A771726 were approached between 6 and 12 hours. Based on determination of A771726, the bioavailability of leflunomide from a tablet formulation relative to an oral solution was 80%. Leflunomide administered with a high fat/high carbohydrate meal was bioequivalent to administration under fasted conditions.

Distribution

In studies with plasma samples obtained from healthy subjects, A771726 was extensively bound to protein (> 99%) (albumin). The unbound fraction of A771726 was 0.62%. Binding of A771726 was linear up to 573 mcg/mL. Compared to healthy subjects, the unbound fraction was slightly increased (0.80%) in plasma from patients with rheumatoid arthritis and was approximately doubled in patients with chronic renal insufficiency. The extensive protein binding of A771726 is consistent with its low volume of distribution. After independent intravenous administration of A771726, steady-state volume of distribution averaged 11 L.

Metabolism

Following oral administration, leflunomide is rapidly converted to the active metabolite, A771726. Animal studies suggest that conversion takes place during passage through both the gut wall and the liver.

The metabolic biotransformation of A771726 is not controlled by a single enzyme and has been shown to occur in microsomal and cytosolic cellular fractions.

The urinary metabolites were primarily glucuronide conjugates of leflunomide and an oxanilic acid derivative of A771726, while A771726 was the primary metabolite in the feces.

Elimination

After oral administration of a 100 mg dose of ^{14}C-leflunomide to healthy volunteers, urinary and fecal recovery of ^{14}C-leflunomide over 28 days accounted for 43% and 48% of total radioactivity, respectively. Unchanged leflunomide was not detected in urine or feces. A771726 is cleared by slow excretion in feces, probably by biliary elimination and slow metabolism to the oxanilic acid metabolite excreted in urine.

After independent intravenous administration of A771726, clearance averaged 31 mL/hr and elimination half-life 10 days. A similar clearance estimate (29 ± 17 mL/hr) was obtained from population pharmacokinetics analysis of rheumatoid arthritis patients enrolled in pivotal safety and efficacy studies.

After single doses of leflunomide to healthy subjects, plasma concentrations of A771726 declined monoexponentially, with a half-life of approximately 8 days. After 24 weeks, the elimination half-life averaged 14 to 18 days.

The elimination half-life in patients is approximately 2 weeks. Oral administration of activated charcoal or cholestyramine is effective in enhancing the elimination of A771726. During oral administration of activated charcoal (50 g four times a day) or cholestyramine (8 g three times a day), the half-life of A771726 decreased to approximately 24 hours. Although the mechanism for the enhanced elimination is unknown, it may be related to interruption of enterohepatic recycling and/or dialysis across the gastrointestinal mucosa.

Special Populations and Conditions

- **Renal Insufficiency**

  When subjects with end-stage renal disease were administered a single 100 mg dose of leflunomide orally, plasma concentrations of A771726 both prior to and after dialysis (chronic ambulatory peritoneal dialysis [CAPD] or hemodialysis) were comparable to those of healthy volunteers administered the same dose. With hemodialysis, A771726 was cleared somewhat more rapidly and with a shorter half-life. The pharmacokinetic parameters for the CAPD patients were consistent with the values for healthy volunteers.

11 Storage, Stability, and Disposal

Store at 15°C to 30°C, in a dry place. Protect from light. Keep out of reach and sight of children.

Part 2: Scientific Information

13 Pharmaceutical Information

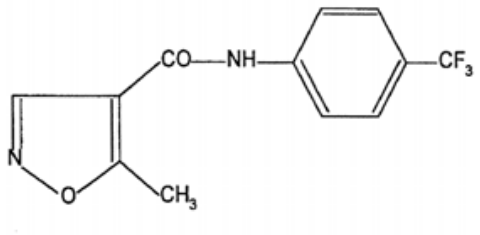
Drug Substance

Non-proprietary name of the drug substance: Leflunomide

Chemical name: N-(4'trifluoromethylphenyl)-5-methylisoxazole-4 carboxamide

Molecular formula and molecular mass: $C_{12}H_9F_3N_2O_2$ and 270.2 g/mol

Structural formula:



Physicochemical properties: Leflunomide is a white to almost white powder. Leflunomide is practically insoluble in water and aqueous buffer systems. Leflunomide is freely soluble in methanol, ethanol, isopropanol, ethyl acetate, propylene carbonate, acetone and acetonitrile. pKa values: 10.8 at 23°C. Melting point between 165 and 167°C.

14 Clinical Trials

14.1 Clinical Trials by Indication

Treatment of active rheumatoid arthritis

Table 4 - Summary of patient demographics for clinical trials in Rheumatoid Arthritis

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
US301	placebo-controlled, 3:2:3 randomization basis to 1 of 3 treatment arms	20 mg, ORAL, 52 weeks leflunomide 20 mg/day after a loading dose of 100 mg/day for 3 days, (2) placebo, or (3) methotrexate 7.5 mg/week or escalation to 15 mg/week, 52 weeks	511	54.1 ± 12.0	M/F
MN301/ MN303/ MN305	randomized on a 3:2:3 basis to 1 of 3 treatment arms	(1) leflunomide 20 mg/day after a loading dose of 100 mg/day for 3 days, (2) placebo, (3) sulfasalazine 2.0 g/day, 24 weeks	358	58.3 (10.6)	M/F
MN302/ MN304	randomized	leflunomide 20 mg/day or methotrexate at 7.5 mg/week increasing to 15 mg/week, 52 weeks	999	58.3+10.1	M/F
MN304	randomized	Leflunomide 20 mg/day or methotrexate at 7.5 mg/week increasing to 15 mg/week, 52 weeks	612		

The efficacy and safety of leflunomide in the treatment of rheumatoid arthritis was demonstrated in two placebo-controlled pivotal clinical studies. For these studies, summaries of the results are presented for the "ACR Success Rates" per treatment group, "ACR Responder Rates" over time, X-ray evaluation of disease progression, and health-related quality of life measures. An "ACR Success", based upon the American College of Rheumatology (ACR) criteria, is a patient who completes the trial and is an ACR Responder at the trial endpoint. An "ACR Responder" is a patient with ≥ 20% improvement in both tender and swollen joint counts and in 3 of the following 5 criteria: [i] physician global assessment, [ii] patient global assessment, [iii] function/disability measure Health Assessment Questionnaire (HAQ) or Modified HAQ (MHAQ), [iv] visual analog pain scale, and [v] erythrocyte sedimentation rate (ESR) or C- reactive protein (CRP). Improvements in function/disability and health-related quality of life were measured by the HAQ, the MHAQ, the Problem Elicitation Technique (PET), and the Medical Outcomes Survey Short Form 36 (SF-36).

Study US301 enrolled 511 subjects with active rheumatoid arthritis of at least 6 months duration, using a 3:2:3 randomization to one of the following 3 groups: (1) Leflunomide 20 mg/day after a loading dose of 100 mg/day for 3 days, (2) placebo, or (3) methotrexate 7.5 mg/week or escalation to 15 mg/week. Treatment duration was 52 weeks. Of the patients who completed the first 12 months of study US301, 235 continued into a second 12 months of double-blind treatment. Leflunomide dose continued at 20 mg/day and the methotrexate dose could be increased to a maximum of 20 mg/week. 190 patients completed 2 years of double-blind treatment.

Study MN301/303/305 enrolled 358 subjects with active rheumatoid arthritis with at least 6 tender joints and 6 swollen joints. Patients were randomized on a 3:2:3 basis to 1 of 3 treatment arms: (1) Leflunomide 20 mg/day after a loading dose of 100 mg/day for 3 days, (2) placebo, (3) sulfasalazine 2.0 g/day. Treatment duration was 24 weeks. Study MN303 was a 6-month blinded continuation of MN301 resulting in a 12-month comparison of the MN301 leflunomide and sulfasalazine treatment groups. 146 of 168 patients who completed the 12 months of treatment in study MN303 entered the double-blind, 1-year extension study MN305. Patients continued on the same daily dosage of leflunomide or sulfasalazine that they had been taking at the completion of MN303. 116 patients completed 2 years of double-blind treatment.

Study MN302/304, a clinical trial complementary to study US301, randomized 999 subjects with active RA to leflunomide 20 mg/day or methotrexate at 7.5 mg/week increasing to 15 mg/week. Treatment duration was 52 weeks. 612 of the 736 patients who completed 12 months of treatment in study MN302 entered the double-blind, 1-year extension study MN304. Patients continued on the same daily dosage of leflunomide or methotrexate that they had been taking at the completion of MN302. 497 patients completed 2 years of double-blind treatment.

Study Results

Table 5 - Summary of ACR Response Rates*

Study and Treatment Group	ACR20	ACR50	ACR70
Placebo-Controlled Studies			
US301 (12 months)			
Leflunomide (n=178)†	52.2‡	34.3‡	20.2‡
Placebo (n=118)†	26.3	7.6	4.2
Methotrexate (n=180) †	45.6	22.8	9.4
MN301 (6 months)			
Leflunomide (n=130) †	54.6‡	33.1‡	10.0§
Placebo (n=91) †	28.6	14.3	2.2
Sulfasalazine (n=132) †	56.8	30.3	7.6
Non-Placebo Active-Controlled Studies			
MN302 (12 months)			
Leflunomide (n=495) †	51.1	31.1	9.9
Methotrexate (n=489) †	65.2	43.8	16.4

* 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 6 - Mean Change in the Comparison of the ACR Responder Index*

Components	Placebo-Controlled Studies						Non-Placebo Controlled Study	
	US301 (12 months)			MN301 Non-US (6 months)			MN302 Non-US (12 months)	
	Leflu-nomide	Metho-trexate	Placebo	Leflu-nomide	Sulfa-salazine	Placebo	Leflu-nomide	Metho-trexate
Tender joint count[1]	-7.7	-6.6	-3.0	-9.7	-8.1	-4.3	-8.3	-9.7
Swollen joint count[1]	-5.7	-5.4	-2.9	-7.2	-6.2	-3.4	-6.8	-9.0
Patient global assessment[2]	-2.1	-1.5	0.1	-2.8	-2.6	-0.9	-2.3	-3.0
Physician global assessment[2]	-2.8	-2.4	-1.0	-2.7	-2.5	-0.8	-2.3	-3.1
Physical function / disability (MHAQ/HAQ)	-0.29	-0.15	0.07	-0.50	-0.29	-0.04	-0.37	-0.44
Pain intensity[2]	-2.2	-1.7	-0.5	-2.7	-2.0	-0.9	-2.1	-2.9
Erythrocyte Sedimentation rate	-6.26	-6.48	2.56	-7.48	-16.56	3.44	-10.12	-22.18
C-reactive protein	-0.62	-0.50	0.47	-2.26	-1.19	0.16	-1.86	-2.45
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

[1] Based on 28 joint count

[2] Visual Analog Scale – 0= Best; 10= Worst

ACR Responder Rates

ACR Success Rates for the placebo-controlled pivotal studies (including MN303 extension of MN301) are shown in Figure 1. Leflunomide was statistically significantly superior to placebo in reducing the signs and symptoms of rheumatoid arthritis by the primary efficacy analysis, ACR Success Rate. ACR Success Rates with leflunomide treatment were consistent across the 6 and 12 month studies (41 to 49%).

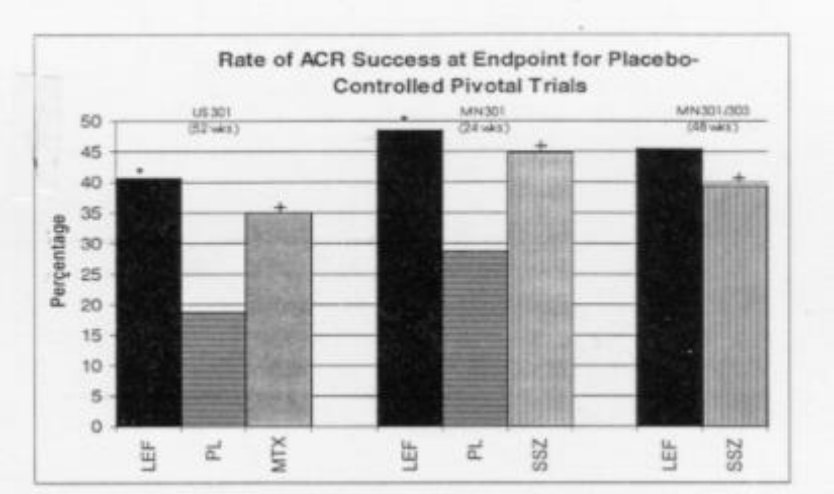


Figure 1.

*p ≤0.01 Leflunomide vs. placebo
+ Active comparator statistically equivalent to Leflunomide
LEF = leflunomide
MTX = methotrexate
PL = placebo
SSZ = sulfasalazine

ACR Responder Rates over time in the placebo-controlled pivotal studies are shown in Figures 2 and 3. Leflunomide was statistically significantly superior to placebo in all efficacy measures including ACR Responder Rate and all individual components of the ACR Responder criteria (tender joint count, swollen joint count, patient and physician global assessments, pain intensity assessment, HAQ or MHAQ, and ESR or CRP) as well as morning stiffness and rheumatoid factor levels. Leflunomide treatment effect was evident by 1 month, stabilizing by 3 to 6 months, and continuing throughout the course of treatment. ACR Responder Rates at end of study with leflunomide treatment were consistent across the 6 and 12 month studies (52 to 55%).

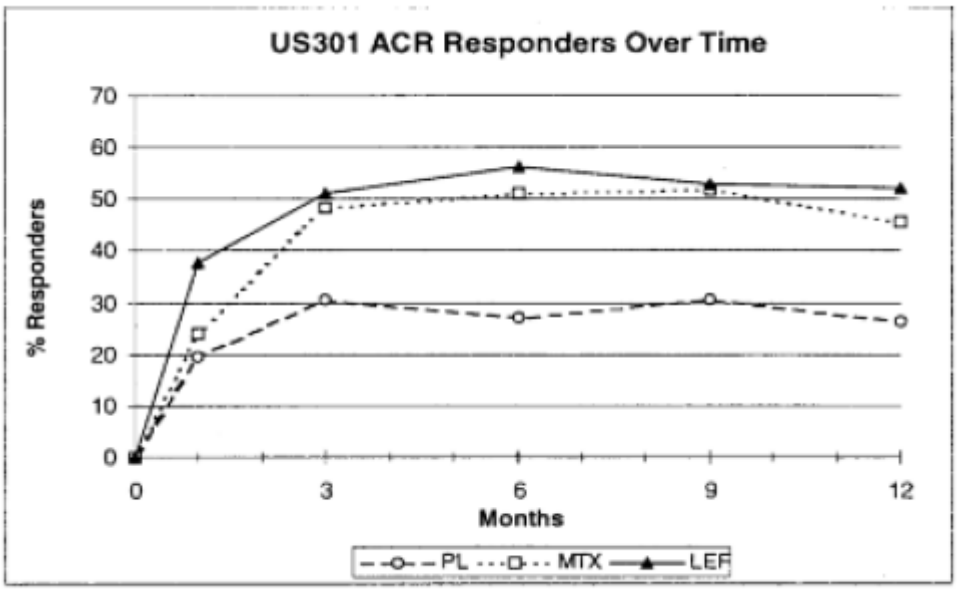


Figure 2

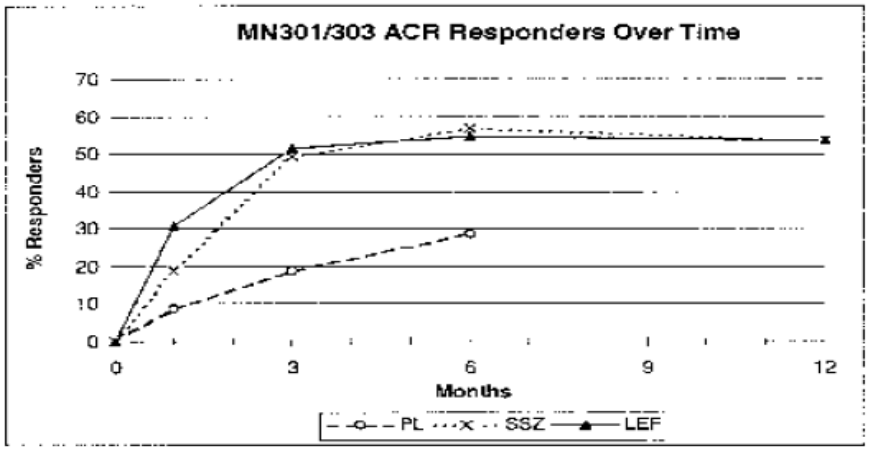


Figure 3

After completing 12 months of treatment in the original pivotal studies, patients were evaluated for an additional 12 months of double-blind treatment (total treatment period of 2 years) in studies US301, MN305, and MN304. Improvement in the ACR response demonstrated at 6 and 12 months was maintained over two years. In addition, in a placebo-controlled dose ranging study enrolling 402 subjects with active rheumatoid arthritis, leflunomide 5 mg/day was not effective; whereas leflunomide 10 mg/day and 25 mg/day were statistically significantly superior to placebo. ACR Responder Rates at endpoint for 10 mg and 25 mg doses were consistent with those in the placebo-controlled pivotal clinical studies.

X-ray Findings

Results of the analyzed Sharp X-ray scores for the two placebo-controlled pivotal studies (including MN303 extension of MN301) are shown in Table 7. Leflunomide was statistically significantly superior to placebo in retarding disease progression as measured by x-ray analysis of both erosions and joint space narrowing. The retarding of progression of erosive disease by leflunomide treatment was further evidenced by statistically significant decreases in the percentage of patients with progression of erosions compared to placebo (US301 3% vs. 12%, and MN301 3% vs. 16%). Thirty percent of patients did not have paired X-rays and sensitivity analyses were required to support the validity of the results. There was a lack of correlation between changes in X-rays and changes in clinical assessments.

Table 7. Analysis of X-rays by Sharp Scores

	US301-12 mos			**MN301-6 mos**			**MN301/303-12 mos**		
	Mean change in Total Score	Mean change in erosion subscore	Mean change in joint space narrowing subscore	Mean change in Total Score	Mean change in erosion subscore	Mean change in joint space narrowing subscore	Mean change in Total Score	Mean change in erosion subscore	Mean change in joint space narrowing subscore
LEF	0.53±4.5*†	0.23±2.20*	0.31±2.78*	-0.06±12.3*	0.17±4.50*	0.22±8.02*	0.90±5.3	0.74±2.18	0.16±3.98
PBO	2.16±4.0	0.89±1.87	1.27±2.69	5.60±9.83	1.97±4.02	3.63±7.31	--	--	--
MTX	0.88±3.3	0.47±1.83	0.41±1.81	--	--	--	--	--	--
SSZ	-	-	-	1.44±13.0	0.78±3.56	0.66±9.73	1.46±13.0	0.92±3.76	0.54±9.69

* p ≤0.05 Leflunomide vs. placebo

† p ≤0.05 Leflunomide vs. active control

LEF= leflunomide, SSZ= sulfasalazine, PBO= placebo, MTX= methotrexate

As demonstrated in placebo-controlled pivotal studies, leflunomide reduces pain, articular swelling and tenderness, and ameliorates the signs and symptoms of rheumatoid arthritis. Joint damage as assessed by X-ray analysis of joint space narrowing and erosions may be retarded by leflunomide compared to placebo at the end of one year of therapy, but no consistent differences were noted between leflunomide and methotrexate or leflunomide and sulfasalazine on assessments of joint damage.

Physical function

The Health Assessment Questionnaire (HAQ) assesses disease-specific physical function and degree of disability in patients - (dressing, rising, eating, walking, hygiene, reach, grip and activities). The HAQ Disability Index (HAQ DI) uses the scores of the worst items within each of the eight categories, modified by the use of devices and aids.

The mean change from baseline in the HAQ Disability Index in the 6 and 12 month placebo and active controlled trials is shown in Figure 4 below.

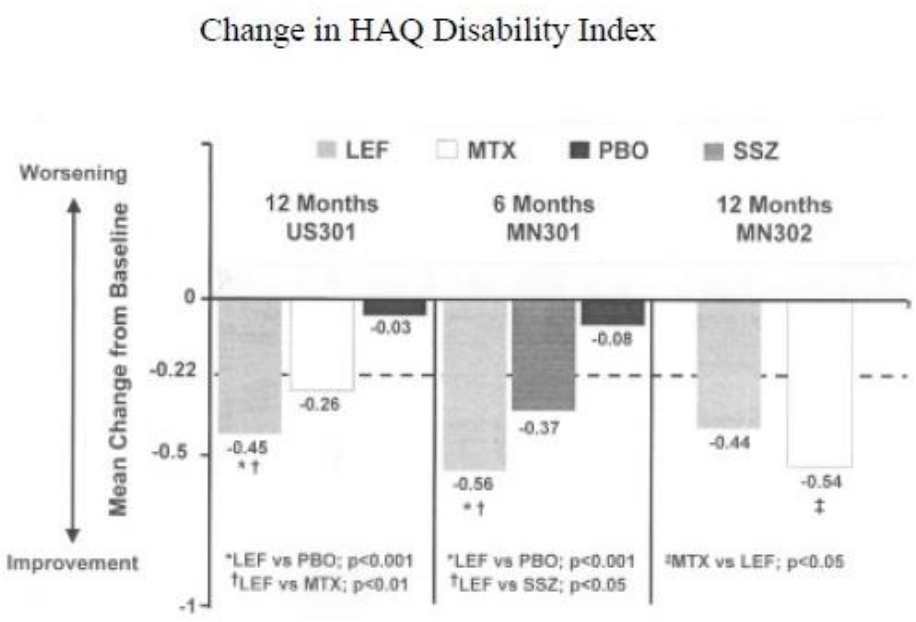


Figure 4 MX: Methotrexate, SSZ: Sulfasalazine, LEF= leflunomide, PBO= placebo

Leflunomide was statistically significantly superior to placebo in improving physical function from baseline to endpoint as assessed by the HAQ Disability Index. The magnitude of improvement in all subscales in the leflunomide treated group was clinically significant, i.e. exceeded the 0.22 unit change threshold. Superiority to placebo was demonstrated consistently across all eight HAQ sub-domains in both placebo controlled studies.

The improvement in physical function and disability demonstrated at 6 and 12 months was maintained over two years, as shown below in Figure 5. In patients continuing leflunomide for a second year of double-blind treatment in US301, MN301-305 and MN302-304, marked, clinically meaningful improvement from baseline in HAQ Disability Index continued to be documented at 24 months in all three trials with no clinically meaningful differences between month 12 and month 24.

Change in HAQ Disability Index - Year-2 cohort

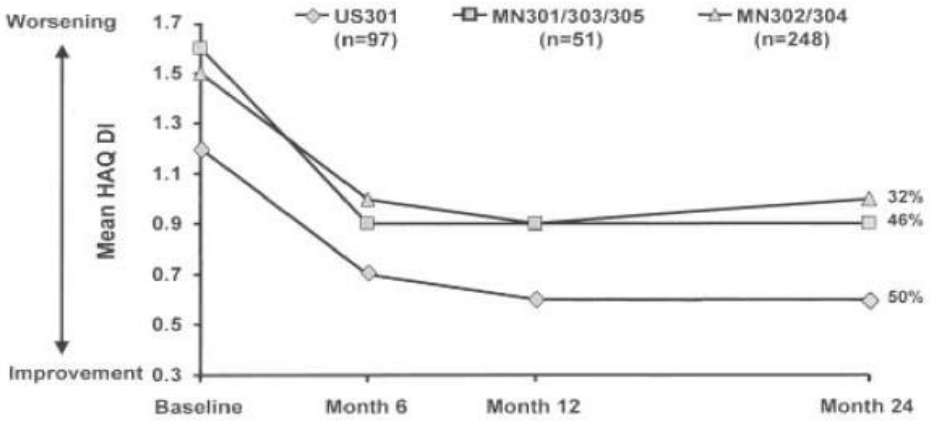


Figure 5

The Health Outcomes Survey Short Form 36 (SF-36) is a generic instrument that assesses physical function as well as social and emotional function. In US301, at 12 months, leflunomide provided statistically significant improvements compared to placebo in 5 of 8 SF-36 scales (physical functioning, pain, general health perception, vitality, and social functioning), the physical component score, and the work productivity score based on work limitations questionnaire. The improvement in physical and emotional functions, as measured by the SF-36, was maintained from 12 to 24 months for subjects treated with leflunomide as shown in Figure 6.

Change in SF-36, Year-2 Cohort

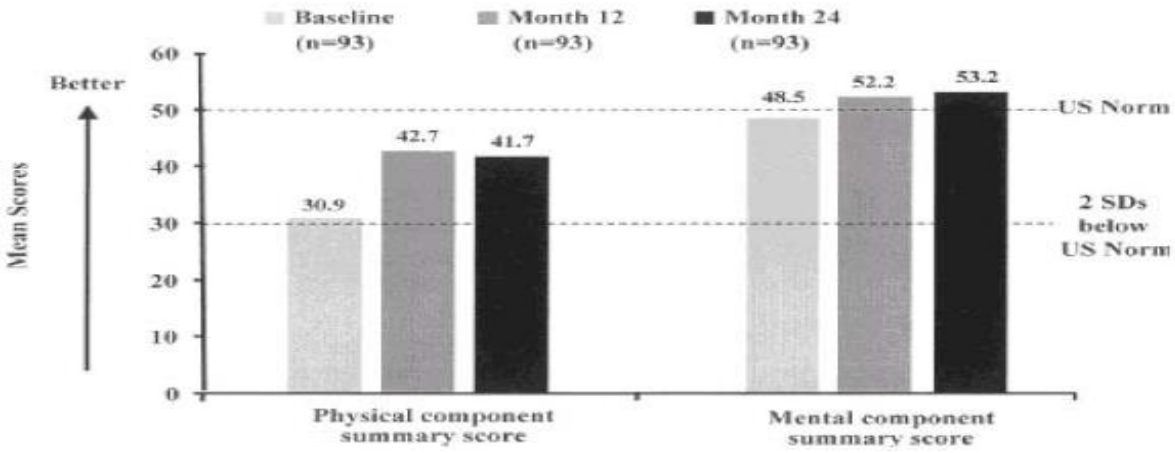


Figure 6

14.2 Comparative Bioavailability Studies

A comparative bioavailability study was performed on healthy human volunteers under fasting

conditions. The rate and extent of absorption of leflunomide was measured and compared following a single oral 20 mg dose of APO-LEFLUNOMIDE (leflunomide) or ARAVA® tablets. The results from measured data are summarized as follows:

Table 8 – Summary Table of the Comparative Bioavailability Data

Leflunomide metabolite A771726 (1 x 20 mg) From measured data under fasting conditions Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test (APO-LEFLUNOMIDE)**	**Reference***	**% Ratio of Geometric Means****	**Confidence Interval 95%**
AUC_{0-72} (ng·h/mL)	96449 97397 (15)	96019 96886 (14)	100.3	97.9 - 102.7
AUC_I (ng·h/mL)	434772 445888 (24)	442937 460783 (30)	97.2	83.6 - 112.9
C_{max} (ng/mL)	1873 1895 (17)	1791 1812 (16)	104.4	100.5 - 108.5
T_{max}§ (h)	1.44 (37)	2.13 (52)		
T½§ (h)	202.2 (29)	209.8 (33)		

* ARAVA® Aventis Pharma Inc. was purchased in Canada
** based on the least squares estimate
§ expressed as arithmetic mean (CV%) only.

Table 9 – Summary Table of the Comparative Bioavailability Data

Leflunomide metabolite A771726 (1 x 20 mg) From measured data under fed conditions Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test (APO-LEFLUNOMIDE)**	**Reference***	**% Ratio of Geometric Means****	**Confidence Interval 95%**
AUC_{0-72} (ng·h/mL)	91108 91696 (12)	95137 96148 (15)	95.7	92.2 - 99.3
AUC_I (ng·h/mL)	350592 365363 (30)	421937 452580 (44)	89.3	70.6 - 112.9

Leflunomide metabolite A771726 (1 x 20 mg) From measured data under fed conditions Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test (APO-LEFLUNOMIDE)**	**Reference***	**% Ratio of Geometric Means****	**Confidence Interval 95%**
C_{max} (ng/mL)	1618 1630 (12)	1694 1715 (16)	95.5	90.0 - 101.5
T_{max}§ (h)	5.22 (76)	6.39 (69)		
T½§ (h)	170.3 (33)	221.5 (59)		

* ARAVA® Aventis Pharma Inc. was purchased in Canada

** based on the least squares estimate

§ expressed as arithmetic mean (CV%) only.

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

Acute Toxicity

Table 10 – List of Acute Toxicity Studies for Leflunomide and its Metabolites

Test Compound	**Species**	**Dose (mg/kg body weight) Route**	**LD_{50} (mg/kg body weight) - Observations**
Leflunomide	Mouse	200, 500 – p.o. 200, 400 – i.p.	between 200 and 500 **Mortality**: At 500 mg/kg death occurred within 24 hrs. **Symptoms**: Reduced activity, lacrimation, trembling. **Pathology**: Lightly coloured kidneys in one animal that dies.

Test Compound	Species	Dose (mg/kg body weight) Route	LD_{50} (mg/kg body weight) - Observations
	Rat	100, 250 - p.o.	between 100 and 250 **Mortality**: 1/4 (100 mg/kg), 3/4 (250 mg/kg), deaths occurred between 4-10 days. **Symptoms**: Panting, reduced activity (100 mg/kg); stilted gait, reduced activity (250 mg/kg). **Pathology**: Stomach and chest filled with fluid, firm livers with uneven surfaces in rats that dies, no changes in rats surviving 3 weeks.
		200, 400 - i.p.	between 200 and 400 **Mortality**: 1/4 (200 mg/kg), 4/4 (400 mg/kg). The intraperitoneal LD_{50} was between 200 and 400 mg/kg. Death occurred between 2-19 days after administration. **Symptoms:** Reduced motility, bristling fur, crawling, squatting (400 mg/kg). **Pathology**: Discoloured livers, reddish small intestinal mucosa, remnants of test material in abdomen in rats that died. No changes in rats that survived to 3 weeks.
Metabolites			
A77 1726	Mouse	100, 200 – p.o.	between 100 and 200 **Mortality:** At 200 mg/kg death occurred between 6 and 8 days post doses. **Symptoms:** 200 mg/kg: reduced motility, bristling fur, transient trembling, crawling, pron position, red-brown discoloured feces, reduced body weight. **Pathology**: No gross pathological changes in surviving animals. Dark red- brown or red discolouration of the bowel contents in the animals which died.

Test Compound	Species	Dose (mg/kg body weight) Route	LD_{50} (mg/kg body weight) - Observations
		100, 160 – i.p.	between 100 and 160 **Mortality:** One death at 100 mg/kg, at 160 mg/kg death occurred within 3 days post dose. **Symptoms:** 100 mg/kg: reduced motility, trembling gait, watery eyes, bristling fur, panting, transient trembling, prone position, red-brown feces. 160 mg/kg: crawling, pronounced flank respiration, diarrhea, transient tremor. **Pathology**: No gross pathologic changes
	Rat	100, 200, 500 - p.o.	between 100 and 200 **Mortality:** At 200 and 500 mg/kg death occurred between 3 and 5 days post dose. **Symptoms:** 200 and 500 mg/kg reduced motility, diarrhea. **Pathology:** Reddish gastric and intestinal mucosa. No changes in rats that survived to 3 weeks.
		63, 100 - i.p.	approximately 100 **Mortality:** At 100 mg/kg death occurred between 2 and 9 days post dosing **Symptoms:** Diarrhea, ruffled fur, trembling or ataxic gait, reduced motility, panting and edema of the iris. **Pathology**: Surviving animals at 100 mg/kg: partly swollen liver lobes, milky coating on liver surface, pale pinhead-sized deposits on liver, No changes in rats that died or received 63 mg/kg.

Test Compound	Species	Dose (mg/kg body weight) Route	LD_{50} (mg/kg body weight) - Observations
Trifluoromethyl-aniline (TFMA)	Mouse	400, 1000 - p.o.	between 400 and 1000 **Mortality:** Occurred within 24 hours in 1/4 mice at 400 mg/kg and 1/1 at 1000 mg/kg. **Symptoms:** Reduced activity, crawling, prone position, increased or irregular respiration, cyanosis and deep necrosis. In the two animals that died, necropsy revealed light-brown or grey lungs. **Pathology**: No gross pathologic changes were found in surviving animals.

Long-Term Toxicity

Table 11 – List of Long-Term Toxicity Studies for Leflunomide and Metabolites

Test Compound	Species	Route	Duration	Dose levels (mg/kg body weight)	Key Observations
Leflunomide	Mouse	p.o.	14 days	0, 15, 30, 60, 100	At 60 and 100 mg/kg mortality occurred in 1/16 and 11/16. Anemia and lower platelet counts and lymphoid atrophy occurred at 30, 60 and 100 mg/kg/day. Also observed in mice given 60 or 100 mg/kg/day were gastro/esophageal ulceration, degeneration and/or atrophy or reproductive organs, and bone marrow hyperplasia or hypocellularity.
		p.o.	14 days	30	Behaviour and general health remained unaffected. TFMA levels ranged from 200 - 350 ng/mL at 2 hours and 70 – 170 ng/mL at 24 hours.
		p.o.	3 months	0, 3, 10, 30	All mice survived to their scheduled necropsy, except 1 male given 3 mg/kg/day and 1 female given 10 mg/kg/day. Males given 10 or 30 mg/kg/day and females given 30 mg/kg/day had higher spleen

Test Compound	Species	Route	Duration	Dose levels (mg/kg body weight)	Key Observations
					weights and spleen-to-body ratios. Mice given 30 mg/kg/day had higher liver weights and ratios. Females given 30 mg/kg/day had lower thymus gland weights and ratios. Increased splenic extramedullary hematopoiesis and hepatocellular centrilobular hypertrophy were present in mice administered 30 mg/kg/day. Mice given 30 mg/kg/day had increased incidence of thymic gland lymphoid atrophy.
	Rat	p.o.	14 days	0, 10, 16, 25	Mortality occurred in 2 rats given 25 mg/kg/day with all other rats surviving to scheduled necropsy. Rats given 25 mg/kg/day gained less weight than other groups. Thymus weights were lower in rats given 25 mg/kg/day. Gastric mucosal lesions were present in 1/10 rats at 16/mg/kg and in most rats at 25 mg/kg/day.
		p.o.	3 months	0, 5, 10, 20	Mortality occurred in 2/30, 5/30 and 22/30 rats dosed at 3, 10 or 20 mg/kg/day respectively. Males given 10 mg/kg and males and females given 20 mg/kg gained less weight than controls. Food intake was decreased at 20 mg/kg. Hematology changes at 20 mg/kg included decreased erythrocyte count, hemoglobin, hematocrit and platelet counts beginning after 4 weeks of dosing. Leucocyte counts were lower and neutrophil counts were higher in rats given 20 mg/kg. AST levels were elevated in rats given 20 mg/kg. Increased liver and kidney weights were present at 20 mg/kg and increased spleen weights in females given 10 or 20 mg/kg. Histopathologic changes in rats that died during the treatment period included myocardial and liver necrosis, pulmonary edema, gastrointestinal extravasations of

Test Compound	Species	Route	Duration	Dose levels (mg/kg body weight)	Key Observations
					blood and changes in the gastrointestinal mucosa.
		p.o.	3 months	0, 2, 4, 8	Similar toxicity profile to previous study.
		p.o.	6 months	0, 0, 5, 1, 2, 4	12 animals died in the 4.0 mg/kg dose group and one animal died in the 0.5 mg/kg group. AST values were elevated in the male rats from the 4.0 mg/kg dose group at the end of dosing and at the end of the recovery period. The following findings were obtained uniformly in the ten animals which died and the two which were killed moribund in both higher dose groups; a) marked depletion of hematopoietic cells in the bone marrow, with preserved erythropoiesis and mostly missing thrombopoiesis in the spleen, b) hemorrhages in at least one spinal cord segment, frequently in the lymph nodes examined and in individual animals in the meninges, the gastrointestinal tract and the wall of urinary bladder, c) marked atrophy of the thymus.
	Dog	p.o.	5 days	8, 16	Hyperemia of the gastrointestinal mucosa was found at the autopsy of the dogs receiving 16 mg/kg.
		p.o.	3 months	0, 4, 8, 16	Mortality occurred in 2/6 dogs given 16 mg/kg/day. Symptoms included transient pale mucous membranes at all doses, decreased food intake and body weight (emaciated) and retinal vascular hypoperfusion at 16 mg/kg. Reduced RBCs were noted in one female at the 4 mg/kg dose. Anemia with Heinz bodies was noted at 8 and 16 mg/kg. Increased BUN AST, bilirubin was noted in males at 16 mg/kg. High liver weights, erythroid hypoplasia at 8 and 16 mg/kg. Gastric and/or duodenal ulcers, hepatic necrosis, pale prostate and testes at 16 mg/kg.

Test Compound	Species	Route	Duration	Dose levels (mg/kg body weight)	Key Observations
		p.o.	6 months	0, 0.8, 2.5, 8	Weight decrease (8 mg/kg/day) was noted in the dogs that died. Focal corneal opacities in all groups including controls, more pronounced at 8 mg/kg/day, corneal ulcers were present in some dogs. Extreme extramedullary hemopoiesis and hemosiderosis in spleen, liver, and bone marrow (2.5 – 8 mg/kg/day), endogenous lipopigment in renal tubular epithelium of all dose groups including control.
		p.o.	12 months	0, 0.25, 0.8, 2.5	Symptoms in two animals receiving 2.5 mg/kg/day included reddish and dry skin and alopecia. Pathology and histopathology changes present only in animals necropsied before study end included severe cachexia, exsiccosis and paleness of the skeletal and intestinal musculature. Bone marrow hemopoiesis, severe involution of the thymus and lymphocytic depletion of the spleen. Skeletal muscle and diaphragm exhibited disseminated hypertrophy of fibre diameter and muscle wall of stomach in pyloric region demonstrated infiltration of mononuclear and eosinophilic granulocytic cells. Laboratory changes included decreased RBC, Hb, Hct, Heinz bodies, Howell-Jolly bodies present in erythrocyte, increased reticulocytes.
	Monkey	p.o.	14 days	20	A slight to moderate muscular weakness was observed from day 7 in the male. A moderate decrease in body weight was noted in both animals. A moderate decrease in erythrocyte and increase in reticulocyte was noted in both animals.
		p.o.	30 days	0, 2, 6.3, 20	Toxicity profile similar to previous study.

Test Compound	Species	Route	Duration	Dose levels (mg/kg body weight)	Key Observations
Metabolite					
A771726	Rat	i.v.	30 days	0, 3.2, 8, 20	Mortality in 6/30 rats at 3.2 mg/kg, 12/30 at 8 mg/kg and 27/30 at 20 mg/kg. The no toxic effect level was below 3.2 mg/kg/day. Symptoms included dose-dependent decreased weight gain, decreased food intake, hypoactivity, bloody feces, prone position, poor general condition, poor nutritional state, bristling coat, stilted gait, and pale skin at 20 mg/kg. Dose-dependent laboratory changes included decreased RBC count, Hb, Hct, increase in mean corpuscle volume, normoblasts, polychromasia, Heinz bodies, Howell Jolly bodies, reticulocytosis, decreased platelets, decreased leucocyte counts. Also noted were increased AST, ALT, very low thrombocyte and leucocyte counts, increased coagulation times, increased granulocyte counts (8 mg/kg), increased urea in females at 8 and 20 mg/kg. Intercurrent deaths were generally caused by bacterial infection (Tyzzer`s disease).
	Rat	i.v.	30 days	0, 0.25, 1	Mortality occurred in 2/30 at 1 mg/kg dose. The no effect level was 0.25 mg/kg/day. Symptoms in 2 animals that died included hypoactivity, dragging hind limbs, prone position, and poor general health. Pathology findings only in the 2 animals which died included severe depression of hematopoiesis linked with lethal cerebellar hemorrhage in one and in the other, lethal Tyzzer`s disease with discoloration of liver, bone marrow and urinary bladder, seminal vesicle and prostate decreased in size.
	Dog	i.v.	30 days	0, 0.8, 2.5, 8	No deaths occurred. Symptoms in some animals included diarrhea, pale mucosa of the mouth, slightly

Test Compound	Species	Route	Duration	Dose levels (mg/kg body weight)	Key Observations
					decreased body weight at 8 mg/kg. Toxic hemolytic anemia was observed at 8 mg/kg. In 1 male and 2 females (8 mg/kg) increased erythropoietic proliferation in the bone marrow, pale intestinal muscles, light brown liver, one male had reduced bone marrow fatty tissue.
TFMA	Mouse	p.o.	3 months	0, 10, 32, 100	Mortality occurred in 7/40 at 100 mg/kg/day. Maximum tolerated dose was below 10 mg/kg/day. Symptoms included cyanosis, panting, gasping, poor general health, drawn-in-flanks, reddish urine, prone position, ruffled fur, decreased activity, palpebral closure, ataxic gait, squatting posture (100 mg/kg/day). Decreased RBC count, Hb, Hct, incidence of Heinz bodies, variation of Hb of erythrocytes, increase in total bilirubin, reticulocytosis, decreased platelets, increased leucocyte counts dose dependently. Increased MCV and MCH at 32 or 200 mg/kg/day. Pathology changes noted included discoloration and change in organ size in spleen, liver, lung, and lymph node. Spleen size increased dose dependently. Histopathology changes included dose-dependent siderosis, extramedullary hematopoiesis in spleen. Kupffer cells in liver and tubular epithelia of kidneys.

Carcinogenicity:

Table 12 – Carcinogenicity Studies in Mouse and Rat

Species/Strain No., Sex per Group	Doses (mg/kg/day) Route of Admin. Duration of Treatment	Observations
Mouse/ CD-1 *Group 1*: 50 M, 50 F *Group 2*: 50+16M, 50+16F* *Group 3*: 50+16M, 50+16 F* *Group 4*: 50+16M, 50+16F* *Group 5*: 70+16M, 70+16F	Group 1: 0 mg/kg (control) Group 2: 0 mg/kg (control) Group 3: 1.5 mg/kg/day Group 4: 5.0 mg/kg/day Group 5: 15.0 mg/kg/day PO stomach tube 2-year carcinogenicity study	- increased incidence of absolute and percentage increase deaths in 15.0 mg/kg/day males during the second 12 months of the study - malignant lymphomas more often in 15.0 mg/kg/day dose group males - increase in number of nematodes in lumen of colon in 15.0 mg/kg/day dose group males - bronchio-alveolar adenomas and carcinomas in dosed females and males - statistically significant increases in spleen and brain weights in all dosed males and 5.0 and 15.0 mg/kg/day dose group females - markedly increased incidence of disseminated alopecia in 15.0 mg/kg/day females - equivocal eye lens findings were demonstrated between dosed and control animals - slight but statistically significant increase in erythrocyte count, hemoglobin and hematocrit in all dosed females - statistically significant decrease in MCV in 15.0 mg/kg/day group female - marked increase in Heinz body formation in 15.0 mg/kg/day dose group males and females

Species/Strain No., Sex per Group	Doses (mg/kg/day) Route of Admin. Duration of Treatment	Observations
		- statistically significant decrease in thrombocyte counts in 15.0 mg/kg/day dose group males - statistically significant and mostly dose-dependent treatment related decrease of mean body weight development in 5.0 and 15.0 mg/kg/day dose groups, and at study end, in 1.5 mg/kg/day dose group females
Rat / Wistar *Group 1*: 50 M, 50 F *Group 2*: 50M, 50F *Group 3*: 60 M, 60 F *Group 4*: 60M, 60F *Group 5*: 80M, 80F *Group 6*: 80M, 80F	Group 1: 0 mg/kg (control) Group 2: 0 mg/kg (control) Group 3: 0.50 mg/kg/day Group 4: 1.25 mg/kg/day Group 5: 3.00 mg/kg/day Group 6: 6.00 mg/kg/day PO stomach tube 2-year carcinogenicity study	- mortality increased significantly in the 6.0 mg/kg/day group after 1 year of treatment, especially in males - most animals sacrificed at week 84 showed pathological hematology values indicating bone marrow toxicity. - upon necropsy, males in the 6.0 mg/kg/day dose group showed increased incidence of red discoloration of the testes, epididymis and lymph nodes, white discoloration of the pancreas, red contents of the urinary bladder and softening of the bone marrow - findings in females in the 6.0 mg/kg/day dose group were less pronounced and limited to the lymph nodes and bone marrow. - animals receiving 3.0-6.0 mg/kg/day showed panmyelopathy in the bone marrow, thrombocytopenia and multifocal hemorrhages resulting in death, especially in males

Species/Strain No., Sex per Group	Doses (mg/kg/day) Route of Admin. Duration of Treatment	Observations
		- male animals surviving until study end showed decreased platelet counts in 0.5-3.0 mg/kg/day dose groups and decreased leucocyte counts in 1.25 and 3.0 mg/kg/day dose groups - no changes in bone marrow histology were observed. No significant hematological changes were observed in surviving females. - intercurrently killed rats (control and treatment groups) had pathological values in hematology (anemia, leucopenia or leucocytosis) and very few of the HWA 486 treated animals in addition had Heinz and Howell-Jolly bodies and increased normoblasts - at 6 mg/kg a severe thrombocytopenia which resulted in prolonged coagulation time and hemorrhages was noted.

* 16 male and 16 female animals from groups 2-5 served as satellite animals for toxicokinetic examinations.

Mutagenicity

Testing of leflunomide, with and without metabolic activation, has yielded consistently negative results in various mutagenicity assays, including point mutation assays with *Salmonella typhimurium* and *E. coli* (Ames test), *in vitro* HGPRT test with V79 Chinese hamster cells, the unscheduled DNA synthesis assay using rat primary hepatocyte cultures, the *in vivo* micronucleus test in NMRI mice, and the *in vivo* chromosomal aberration assay in bone marrow of Chinese hamsters**.**

In contrast, TFMA (the minor metabolite of leflunomide) was found in the literature to be mutagenic in the Ames test but inactive in the unscheduled DNA synthesis assay in rat hepatocytes. Additional mutagenicity testing revealed mutagenic potential *in vitro* in the Ames test, HGPRT test, and *in vitro* chromosomal aberration test in V79 Chinese hamster cells. No mutagenic/genotoxic effects were observed in 2 *in vivo* studies (micronucleus test after ip dosing and chromosomal aberration test in Chinese hamster bone marrow).

Toxicokinetics
Leflunomide was well absorbed and quickly metabolised to the active metabolite A771726 in mouse, rat, dog and man. The conversion to A771726 was virtually completed on first-pass (gut- wall and liver) and parent leflunomide concentrations were only occasionally above the detection limit in plasma. It was not possible to calculate AUC and hence compare exposure to leflunomide across the species.

The metabolite A771726 had a low volume of distribution (10.9 litres in man, 3.5 litres in dog), due to extensive plasma protein binding (> 98% in animals and > 99% in man). The elimination half-lives of A771726 (or total radioactivity which reflected almost exclusively the metabolite A771726), in plasma were 10.6 hours in mouse, 9 hours in rat, approximately 15 to 20 hours in dog and 185 hours in man. There was no evidence for accumulation in rat or dog and in man steady- state plasma concentrations were close to those predicted from single dose data. The following table shows a comparison of the AUC and C_{max} data for A771726 in animals and man upon repeated daily dosing. In rat and dog these data were obtained during toxicity studies whilst the human data was obtained during Phase II studies in rheumatoid patients at dose levels of 5, 10 and 25 mg. There were no significant differences in these parameters between healthy volunteers and rheumatoid patients.

Table 13 – AUC and C_{max} Data Comparison for A771726

Species	Dose (mg/day)	AUC (mcg·h/mL)	C_{max} (mcg/mL) ($C_{24h(ss)}$ for man)
Man	5	211	8.78
	10	432	17.98
	25	1512	63
Mouse	1.5	156	7.5
	5	797	39.2
	15	2380	112
Rat	0.5	4.55	1.58
	1.25	12.8	4
	3	22.1	7.5
	6	39	13.1
Dog	0.25	12.8	1.04
	0.8	54.2	4.22
	2.5	221	16.1

The following table presents the IC_{50}s for the effects of A771726 on DHO-DH activity and cell proliferation in rat, mouse and human.

Table 14

IC_{50} dihydroorotate dehydrogenase (nM)			
	Rat	**Mouse**	**Human**
A771726	16 ± 2	81 ±12	657 ± 46

IC_{50} anti-proliferative activity (mcM)			
A771726	0.14 ± 0.008	16 ± 11	46 ± 6

Reproductive and developmental toxicology:

Leflunomide was teratogenic and caused embryo/fetal death while not causing systemic toxicity or affecting fertility in the parental generation. This was demonstrated in reproductive and developmental toxicity studies with leflunomide in the rat and rabbit.

Conclusions from fertility study

- in the rat, there were no effects on fertility ≤ 4 mg/kg/day
- there were no pre-and postnatal effects at 0.4 mg/kg/day
- leflunomide was teratogenic at ≥ 1.25 mg/kg/day

Conclusions from embryo-fetal/teratogenicity studies

- in the rat, there were no maternal or developmental effects at 1 mg/kg/day
- in the rabbit, there were no maternal effects at ≤ 10 mg/kg/day and no developmental effects at 1 mg/kg/day
- leflunomide was teratogenic at 15 mg/kg/day in the rat and 10 mg/kg/day in the rabbit

Conclusions from peri/postnatal studies

- in the rat, there were no maternal effects ≤ 1.25 mg/kg/day
- there were developmental effects at 0.4 mg/kg/day
- leflunomide was teratogenic at 4 mg/kg/day

Conclusions from in vitro study

- leflunomide and its major metabolite were teratogenic
- A771726 (metabolite) was twice as active as HWA 486 (parent compound)

Conclusions from Toxicokinetic Studies

- in the rabbit, there was no clear relation of T_{max} at the dose level or number of administrations
- only at the 10 mg/kg (as opposed to 1 mg/kg) dose level was any effect of repeat dosing observed.

Table 15 – Reproduction and Teratology Studies

Segment	Species/Strain	Initial Group	Mode of Admin.	Doses mg/kg/day
I	Wistar Rat	32 M, 32 F (each group)	PO	- LEF 0, 0.4, 1.25 or 4 mg/kg for last 70 days (M) and last 14 days (F) before mating. Dosing continued in females during pregnancy and lactation period.

Segment	Species/Strain	Initial Group	Mode of Admin.	Doses mg/kg/day
II	Wistar Rat	3-10 F pregnant (each group)	PO	- LEF 5, 10, 15, 20 or 30 mg/kg from the 7th - 16th day of pregnancy
	Wistar Rat	22 F pregnant	PO	- LEF 1 or 15 mg/kg from the 7th - 19th day of pregnancy
	Himalayan Rabbit	2-11 F pregnant	PO	- LEF 5, 10, 15, 16, 20, 25 and 30 mg/kg from the 6th - 18th day of pregnancy
	Himalayan Rabbit	20 F pregnant	PO	- LEF 0, 1 or 10 mg/kg from the 6th - 18thth day of pregnancy
	Himalayan Rabbit*	15 F pregnant (3 groups of 5 each)	PO	- A771726 0.1 and 10 mg/kg/day from Day 6 to Day 17 of pregnancy
in vitro	Sprague Dawley (strain not reported) Cells from 13-day old rat embryos	from 10 mated female rats	IV	- LEF 0.25, 0.5, 1, 2, 4, 8, 16, 31, 62, 125 and 250 mcg/mL - A771726 0.25, 0.5, 1, 2, 4, 8, 16, 31, 62, 125 and 250 mcg/mL
III	Wistar Rat	20 F	PO	- LEF 0, 0.4, 1.25 or 4 mg/kg from Day 7 after mating to Day 21 after parturition

* Toxicokinetic study in Himalayan Rabbit identical to the Segment II rabbit study performed to generate toxicokinetic data in pregnant rabbits.

Detailed Pharmacology

Animal Pharmacology

Autoimmunity Models

In rats, leflunomide dose dependently prevented the symptoms of induced arthritis with a median effective dose (ED_{50}) of 1 to 4.5 mg/kg/day. Leflunomide suppressed radiographically detectable changes in bone structure and periarticular tissues when treatment was started within 12 days of disease induction, and the benefits persisted for as long as 79 days. Mice with such induced disease, however, required about 3 times as much drug as rats to obtain the same efficacy. In antigen-induced monoarticular arthritis in rats, leflunomide (10 mg/kg/day, po)

administered during the effector phase produced significant inhibition of the DTH (delayed-type hypersensitivity) inflammation.

Leflunomide reduced the occurrence of chronic secondary lesions in adjuvant-induced arthritis caused by immunopathological mechanisms and was thus comparable to immunosuppressant drugs. In rats with T cell-mediated, allergic encephalomyelitis, a condition with characteristics similar to those of multiple sclerosis, leflunomide and A771726 were effective at dosages of 10 mg/kg/day, po, administered for 17 days. In rats with tubulointerstitial nephritis, a condition with characteristics of autoimmune kidney disorder, leflunomide was effective at dosages of 5 to 10 mg/kg/day, po, administered for 13 days.

In several studies, leflunomide was effective in preventing as well as treating the autoimmune condition, reducing antibody formation and improving survival rates, and the effects continued long after therapy had ceased. In rats administered leflunomide (10 mg/kg/day, po) as collagen-induced arthritis was developing, leflunomide produced significant inhibition of arthritic paw edema, paw lesions, acute phase response, anti-collagen antibodies and collagen dermal Arthus and DTH-like inflammation.

Beginning 17 days after the injection of parental lymphoid cells decreased proteinuria, administration of leflunomide (10 to 30 mg/kg/day, po) lowered immune complex deposition, and lowered the index of GvH (graft versus host) disease evaluated 10 weeks after disease induction. In addition, the response of splenic lymphocytes to mitogen stimulation, which is decreased in diseased animals, was normalized by leflunomide treatment.

Immunomodulatory Models

Studies of immunomodulation included studies of cell-mediated cytotoxicity (a T cell response to antigen), skin transplantation, and Type 1 allergy. Cell-mediated cytotoxicity was inhibited by leflunomide. In mice, leflunomide (50 mg/kg, po or ip) prevented the generation and proliferation of antigen-induced cytotoxic T lymphocytes, although A771726 did not interfere directly in the natural killer cytotoxicity of human peripheral blood mononuclear cells (PBMC) against K-562 target cells. In mice, leflunomide (12.5 mg/kg/day, po; 25 to 100 mg/kg/day, ip) and A771726 (10 to 20 mg/kg/day, po; 10 mg/kg/day, ip) inhibited the T cell-dependent and T cell-independent B cell responses. A771726 inhibited proliferation of B cells and the secretion of IgM, possibly by suppressing the expansion of antibody secreting cells or by inhibiting B cell differentiation or secretion. Leflunomide modified the immune system by depressing lymphocyte activity, especially in B cells. Therefore, these agents have immunosuppressive activity in both humoral and cell-mediated responses.

Mechanisms Underlying Anti-Autoimmune and Immunomodulatory Effects

Leflunomide was antiproliferative in *in vitro* experiments using mouse, rat, monkey and human lymphocytes either unstimulated or stimulated with a variety of B and T cell mitogens. Antiproliferation was also seen in transformed but unstimulated murine and human cell lines and in the murine mixed lymphocyte reaction of allogeneic spleen cells. The 50% inhibitory concentration (IC_{50}) values were < 1.0 mM in rat cells, although cells from mice and humans

were less sensitive, with IC_{50} values up to 10.0 mM.

In several species, A771726 dose dependently inhibited proliferation of splenocytes, thymocytes, lymphocytes, and peripheral blood mononuclear cells (PBMC) stimulated by various mitogens and interleukins. A771726 inhibited the expression of the interleukin-2 (IL-2) receptor and the nuclear protein antigens Ki-67 and PCNA in human PBMC. Both of these nuclear proteins are associated with progression into the cell cycle.

In rodent spleen cells, human PBMC, and several cell lines, A771726 blocked lymphocyte activation at a point downstream of initial signalling events. A771726 had similar kinetics on inhibition of proliferation of cells as the immunosuppressant drugs brequinar and rapamycin. However, the mechanism of inhibiting cell cycle progression did not include general protein synthesis.

An important finding related to the effects on the cell cycle was that A771726 is an inhibitor of de novo pyrimidine biosynthesis. A771726 inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH). This enzyme catalyses the conversion of dihydroorotate (DHO) to orotate, the fourth step in de novo biosynthesis of the pyrimidine nucleotides uridine and cytidine. Pyrimidine nucleotides are essential for normal immune cell functions. That inhibition of pyrimidine synthesis underlies the antiproliferative effects of A771726 is evidenced by the following findings in murine systems:

- A771726 failed to block mitogen-induced cell proliferation in the presence but not the absence of uridine.
- Inhibition of the DTH response showed a qualitative relationship with binding affinities of several A771726 analogues and with inhibition of DHODH activity.
- Uridine counteracts inhibition of the graft-versus host reaction.

A771726 IC_{50} values for the recombinant human and rat DHODH enzymes were 1 nM and 19 nM, respectively. Leflunomide was a relatively weak inhibitor of the recombinant human and rat eymes: IC_{50} = 98 nM and 6.3 nM, respectively.

Induction of cell-cycle arrest at the G1/S boundary in T cells treated *in vitro* with A771726 is mediated through DHODH inhibition and subsequent pyrimidine depletion, activating the p53 and p21WAF-1 pathways.

The rank order of IC_{50} values for inhibition of DHODH for the rat, mouse, and human enzymes (16 + 2 nM, 81 + 12 nM, and 657 + 46 nM) parallels the rank order of IC_{50} values for inhibition of cell proliferation (0.14 + 0.08 mcM, 16 + 11 mcM, and 46 + 6 mcM).

Studies of Inflammation

Leflunomide (1-25 mg/kg) had an anti-inflammatory activity similar to NSAIDs in several animal models of inflammation, including ultraviolet (UV)-induced erythema in guinea pigs, carrageenan-induced paw edema, and granuloma formation in response to implantation of cotton pellets in rats. The effectiveness depended on the dose and time of application.

Leflunomide was also effective in rats adrenalectomized 3 days previously, indicating that it did not act by stimulating release of endogenous corticosteroids. Various studies indicated that A771726 reduced arachidonic acid-induced ear edema in mice. Topical application of leflunomide was not effective.

The effects of leflunomide and A771726 on platelet aggregation were weak and variable. The enzymes of arachidonic acid metabolism, phosphorylase A2, 5-lipoxygenase and LTB4-hydrolase, thus are not targets for A771726.

Adherence of leucocytes to endothelium, basement membranes and other surfaces is seen in inflammatory responses. A771726 inhibited adhesion in studies including f-Met-Leu-Phe (FMLP) -induced leucocyte adhesion to rat mesenteric venule endothelium *in vivo*, aggregation of PBMC and spleen-derived mononuclear cells in experimental autoimmune diabetes in mice, and spontaneous and phorbol-ester homotypic adhesion of PBMC and mononuclear cells from synovial fluid of rheumatoid arthritis patients.

Safety Pharmacology

Leflunomide administered intraduodenally (1 to 100 mg/kg) to dogs did not affect cardiovascular parameters. Although leflunomide bears some resemblance to anilines and anilides, which cause methemoglobinemia, at concentrations of 37 to 370 mM leflunomide did not alter methemoglobin production by human whole blood (*in vitro*).

The effect of leflunomide on the gastrointestinal tract was studied in rats. Acute administration of leflunomide to fasted rats produced an ulcerative median dose (UD_{50}) of approximately 33 mg/kg. Under the same conditions the UD_{50} for naproxen was 19 mg/kg and for phenylbutazone was 53 mg/kg. In fed rats that were dosed subacutely with leflunomide for 4 days a UD_{50} of approximately 70 mg/kg was observed.

Oral administration of 20 mg/kg of leflunomide to male Cebus monkeys caused a marked increase in uric acid excretion but did not change the excretion of urine and electrolytes compared to vehicle-treated monkeys.

In a series of experiments in mice and rats, leflunomide (10 to 100 mg/kg, po) had either no or only slight effects on general behaviour, the central nervous system, and the autonomic nervous system.

The effect of leflunomide on respiratory parameters in pentobarbital anaesthetized dogs administered intraduodenal doses of 1, 10, and 100 mg/kg was evaluated. The bronchospasmolytic effects of leflunomide (4 to 15 mg/kg) were specific against bradykinin but not against acetylcholine, histamine or serotonin in anaesthetized guinea pigs.

Leflunomide administered orally at 10, 20 and 40 mg/kg produced no antagonistic effect on reserpine or tetrabenazine-induced ptosis.

The inhibition of *ex vivo* platelet aggregation induced by collagen was evaluated in rabbits following oral doses of 5, 10, 15, 20, and 25 mg/kg of leflunomide. These doses produced a slight to moderate inhibition of platelet aggregation.

Drug Interactions

Rats administered leflunomide (0.1 to 3.0 mg/kg/day, po) with indomethacin (4.25 mg/kg/day, po) administered twice a day for 4 days did not show significantly increased gastrointestinal ulcers or erosions relative to rats receiving indomethacin alone.

In a study of saluresis and diuresis of conventional diuretic drugs in rats, leflunomide was administered at doses of 5, 10, and 20 mg/kg, po, alone and with hydrochlorothiazide (HCT) at 50 mg/kg and furosemide at 25 and 50 mg/kg. Phenylbutazone was used as a reference drug employing doses of 20, 50, and 100 mg/kg.

In rats saline-loaded orally, leflunomide had a slight diuretic effect but no substantial effects on the diuresis induced by HCT or furosemide. Phenylbutazone significantly reduced the diuretic effects of HCT and furosemide. Leflunomide produced a slight reduction in the excretion of Na^+ and Cl^-, but not K^+, but had no additional affect on the activity of HCT and furosemide. In rats saline-loaded intraperitoneally, leflunomide did not significantly induce diuretic effects or affect the diuretic activity produced by HCT or furosemide. In rats with no saline loading, leflunomide produced no diuretic effect alone, and tended to decrease the effect of HCT and slightly decreased the effect of furosemide. Leflunomide did not affect ion excretion alone or in combination with HCT but did increase ion excretion induced by furosemide. Phenylbutazone increased the diuretic activity of both HCT and furosemide.

17 Supporting Product Monographs

1. ARAVA® [Film-coated Tablets, 10 mg and 20 mg], control 302223, product monograph, Sanofi-Aventis Canada Inc. (2026-02-19)

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-LEFLUNOMIDE

Leflunomide Tablets

This Patient Medication Information is written for the person who will be taking **APO-LEFLUNOMIDE**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **APO-LEFLUNOMIDE**, talk to a healthcare professional.

What APO-LEFLUNOMIDE is used for:

APO-LEFLUNOMIDE is used to treat adults who have active rheumatoid arthritis. Rheumatoid arthritis is an immune system disease causing inflammation of the joints.

How APO-LEFLUNOMIDE works:

APO-LEFLUNOMIDE includes the medicinal ingredient, leflunomide. Leflunomide belongs to a group of drugs called immunosuppressants. In rheumatoid arthritis, the immune system produces a chemical in the body that causes inflammation. This causes pain, stiffness, and swelling around the joints. APO-LEFLUNOMIDE works by reducing the body's ability to produce the chemical that is responsible for the inflammation. This helps control the symptoms of rheumatoid arthritis.

The ingredients in APO-LEFLUNOMIDE are:

Medicinal ingredient: leflunomide

Non-medicinal ingredients: anhydrous lactose, colloidal silicon dioxide, crospovidone and magnesium stearate.

APO-LEFLUNOMIDE comes in the following dosage forms:

Tablets, 10 mg and 20 mg.

Do not use APO-LEFLUNOMIDE if:

- you are pregnant, think you are pregnant or able to get pregnant but are not on reliable

birth control. Pregnancy must be excluded before you start treatment with APO-LEFLUNOMIDE;
- you are breastfeeding;
- you have a disease of the liver;
- you are allergic or have ever had an allergic reaction to leflunomide, teriflunomide or any other ingredients in this medicine. Especially a serious skin reaction such as red rash, skin peeling, blisters;
- you have a disorder that impacts your immune system (e.g. AIDS);
- you have a bone marrow problem or if there is a significant decrease in the number of red cells, white cells, or platelets in your blood;
- you have a serious infection;
- you have a moderate to severe kidney disease;
- you have severely low numbers of proteins in your blood (hypoproteinemia);
- you are younger than 18 years of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-LEFLUNOMIDE. Talk about any health conditions or problems you may have, including if you:

- have or had heart disease or heart valve problems.
- have or had blood clots stuck in the lung (pulmonary thromboembolism) or lung disorders (i.e. interstitial lung disease).
- have ever had tuberculosis. If you have ever had tuberculosis, your healthcare professional will monitor you in case the tuberculosis becomes active again.
- are going to have or recently had major surgery, or if you still have a wound that has not yet healed following surgery. APO-LEFLUNOMIDE may affect how a wound heals.

Other warnings you should know about:

Washout Procedures:
Serious side effects might occur and persist, even if the treatment with APO-LEFLUNOMIDE has been stopped. To manage these side effects, your healthcare professional may remove APO-LEFLUNOMIDE from your body by performing a Washout Procedure. Your healthcare professional may also perform a Washout Procedure if you switch to other drugs used to treat rheumatoid arthritis (i.e. Disease-Modifying Antirheumatic Drugs) or if you will be having surgery. This is because APO-LEFLUNOMIDE can stay in your body for a long period of time after you stop taking it.

Stomach and Intestinal Problems (gastrointestinal):
Taking APO-LEFLUNOMIDE may cause gastrointestinal side effects, some can be serious or fatal. Tell your healthcare professional if you have unexplained chronic diarrhoea or weight loss. Your healthcare professional may perform additional tests to determine if you have Colitis.

Nerve problems:
Taking APO-LEFLUNOMIDE may cause nerve problems in your arms or legs. Speak to your healthcare professional immediately if you experience altered sensations, muscle weakness, numbness, tingling or burning in arms or legs. You are at a higher risk of experiencing nerve problems if you are:

- over 60 years of age
- taking neurotoxic medication
- diabetic

Lung Problems:
Taking APO-LEFLUNOMIDE can cause diseases that inflame or scar lung tissue (Interstitial Lung Disease). Interstitial Lung Disease can be fatal. Speak to your healthcare professional if you experience any of the side effects. See 'Possible side effects from using APO-LEFLUNOMIDE'.
The risk of developing Interstitial Lung Disease is higher if you:

- have a disease that affects the lungs and other parts of the respiratory system
- have or had taken drugs that cause Interstitial Lung Disease (i.e. Disease-Modifying Antirheumatic Drugs).

Skin Problems:
Severe skin reactions may occur when taking APO-LEFLUNOMIDE. Speak to your healthcare professional immediately if you experience any of symptoms associated with the severe skin reactions. This includes:

- Stevens-Johnson syndrome
- toxic epidermal necrolysis
- drug reaction with eosinophilia and systemic symptoms (DRESS)
- Skin ulcers

Severe immune system reactions:
Severe immune system reactions may occur when taking APO-LEFLUNOMIDE. Hemophagocytic lymphohistiocytosis (HLH), including macrophage activation syndrome (MAS) is a severe immune system reaction that may be life threatening. HLH/MAS may either develop following DRESS or independently. Symptoms can include a prolonged high fever, extreme tiredness, or swollen glands. If you experience these symptoms, contact your healthcare professional immediately. Early treatment is important and can help you get better.

See 'Possible side effects from using APO-LEFLUNOMIDE' for more information. Your healthcare professional may end your treatment and perform the 'Washout Procedure'

Pregnancy and breastfeeding:

Female patients

- If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional

- Do not take APO-LEFLUNOMIDE if you are, or think you may be pregnant. It may harm your unborn baby and cause serious birth defects.
- Do not breastfeed while you are taking APO-LEFLUNOMIDE
- If you are able to become pregnant:
  - Your healthcare professional will do a pregnancy test before you start taking APO-LEFLUNOMIDE. This test must show that you are not pregnant
  - Use reliable birth control methods when taking APO-LEFLUNOMIDE. Ask your healthcare professional about methods of birth control available to you.
- Speak to your healthcare professional if you plan to become pregnant after stopping treatment with APO-LEFLUNOMIDE. APO-LEFLUNOMIDE need to be eliminated from your body before trying to become pregnant.
  - Once you stop taking APO-LEFLUNOMIDE, you must wait a period of 2 years before trying to get pregnant.
  - This waiting period may be shortened to a few weeks by taking a certain medicine. The medicine will speed up the removal of APO-LEFLUNOMIDE from your body.
  - Speak to your healthcare professional if you are taking an oral contraceptive pill. The medicine that speeds up the removal of APO-LEFLUNOMIDE may lower the effect of your contraceptive pill. You may need another contraceptive method during this period.
  - Two blood tests must be taken two weeks apart to show that APO-LEFLUNOMIDE has been removed from your body.
- Contact your healthcare professional **immediately** if you suspect that you are pregnant while taking APO-LEFLUNOMIDE or in the two years after you have stopped treatment.
  - You must have a pregnancy test at the first delay of your period. If the test confirms that you are pregnant, your healthcare professional will discuss the potential risks to your unborn baby.
  - Your healthcare professional may suggest treatment with certain medicines to remove APO-LEFLUNOMIDE from your body. This treatment may reduce the risk to your baby.

Male patients

- Avoid fathering a child while you are taking APO-LEFLUNOMIDE or two years after your treatment. It may harm your unborn baby and cause serious birth defects.
- During your treatment with APO-LEFLUNOMIDE, use a reliable birth control each time you have sex with a woman who is pregnant, may be pregnant or could get pregnant. Ask your healthcare professional about methods of birth control available to you.
- If you wish to father a child
  - During your treatment, your healthcare professional may stop treatment and advise you to take a certain medicine. The medicine will speed up the removal of APO-LEFLUNOMIDE from your body.
  - After your treatment, inform your healthcare professional beforehand. You must wait a period of 2 years before trying to father a child. This waiting period may be shortened by taking a certain medicine that will remove APO-LEFLUNOMIDE from

your body.
    - Two blood tests must be taken to show that APO-LEFLUNOMIDE has been removed from your body. You should then wait for another 3 months before you try to get your partner pregnant.
- If, during your treatment with APO-LEFLUNOMIDE or you have taken it within the last 2 years, your sexual partner becomes pregnant or thinks she may be pregnant, tell your healthcare professional right away.

Check-ups and testing: You will have regular visits with your healthcare professional, before and during your treatment. They will:

- Check your liver function as APO-LEFLUNOMIDE may cause liver problems
- Check your lungs. Taking APO-LEFLUNOMIDE may cause areas of abnormal growth on your lungs. This condition may not cause symptoms and can be identified by your healthcare professional through imaging scans.
- Check your blood pressure
- Do blood tests to monitor blood cell levels.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-LEFLUNOMIDE:

- activated charcoal
- cholestyramine
- cimetidine (stomach acid medicine)
- duloxetine (anti-depressant)
- Certain disease modifying antirheumatic (DMARDs) including gold (taken by mouth or by injection into the muscle), penicillamine, methotrexate, or azathioprine
- phenytoin
- teriflunomide
- theophylline (asthma medicine)
- tizanidine (muscle relaxant medicine)
- warfarin
- medicines used to treat diabetes, such as: repaglinide, pioglitazone, rosiglitazone, nateglinide or tolbutamide
- oral contraceptives
- some medicines used to treat infections such as: antimalarial drugs, cefaclor, ciprofloxacin, penicillin G, rifampin, rifampicin, zidovudine
- medicines used to lower blood cholesterol, such as: rosuvastatin, atorvastatin, simvastatin, pravastatin
- anti-inflammatory drugs, such as: indomethacin, ketoprofen, sulfasalazine
- diuretics (water losing pills), such as: furosemide

- some medicines to treat cancer such as: paclitaxel, methotrexate, topotecan, daunorubicin, doxorubicin
- medicines used to relieve pain and inflammation such as nonsteroidal anti-inflammatory drugs (NSAIDs) or cortisone. APO-LEFLUNOMIDE can be taken with these medicines. Your healthcare professional will give you specific instructions about these medicines.

What you should avoid while taking APO-LEFLUNOMIDE:

- It is not recommended to drink alcohol during treatment with APO-LEFLUNOMIDE.
- You must not receive any type of live vaccinations while taking APO-LEFLUNOMIDE or within 6 months after stopping treatment. Check ahead with the clinic if you have to be vaccinated

How to take APO-LEFLUNOMIDE:

- Always take APO-LEFLUNOMIDE exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Swallow tablets whole, with water or another fluid.
- Take with or without food. Take it at the same time every day

Usual dose:

Recommended starting dose: 100 mg once daily for the first 3 days

Maintenance dose: 20 mg once daily. The dose may be reduced to 10 mg once daily, depending on the side effects experienced. Your dose could also be temporarily stopped if you need surgery.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-LEFLUNOMIDE, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you missed a dose of this medication, take it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Do not take two doses at the same time.

Possible side effects from using APO-LEFLUNOMIDE:

These are not all the possible side effects you may have when taking APO-LEFLUNOMIDE. If you experience any side effects not listed here, tell your healthcare professional.

- abdominal or back pain,
- abnormal skin sensations like tingling
- cough, sore throat, congested nose and sinus,
- diarrhea
- dry or itchy skin
- eczema
- headache,
- increased hair loss
- joint pain or inflamed
- leg cramps
- nausea (queasiness),
- vomiting,
- weight loss (usually mild),
- weakness
- wounds that take longer to heal

APO-LEFLUNOMIDE can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment.

Serious side effects and what to do about them

Frequency/Side effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Common			
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		√	

Frequency/Side effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Gastrointestinal problems: diarrhea, vomiting, dehydration, constipation, having gas, severe weight loss (anorexia), blood in stool, bloody vomit, black tarry stools		√	
Loss of appetite	√		
Mouth sores or ulcers: the appearance of round lesions that have red edges and are yellow, white, or gray in the middle, difficulty eating or drinking, fever		√	
Pain and swelling of the tendon	√		
Skin rash: as painful blister, red rash spreading and skin peeling			√
Uncommon			
Blood problems (low white or red blood cells or platelets): shortness of breath, weakness, frequent infections, cold sores, pale skin, rapid heart rate, fatigue, fever, bruising easily, heavy bleeding or bleeding for longer than usual if you hurt yourself		√	
Eye disorders: lazy eye, dimness of vision, eye infection, cataract, pink eye		√	
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		√	

Frequency/Side effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Diabetes (condition where the body does not produce enough insulin): excessive eating, thirst, and urination; unexplained weight loss, poor wound healing, infections		√	
Heart related problems: chest pain, irregular, fast heart beat, widening of blood vessels, varicose veins (enlarged twisted veins)		√	
Infection (including infection of the blood that can be fatal): fever and chills, nausea, vomiting, diarrhea, little or no urine, low blood pressure, palpitations, rapid breathing, rapid heartbeat, generally feeling unwell		√	
Liver problems including Hepatotoxicity and hepatic necrosis: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, light-colored stool, fever, unusual tiredness			√
Lung problems including Interstitial lung disease and Pneumonia (diseases that infect, inflame or scar lung tissue): shortness of breath when rest that gets worse with exertion, dry cough, cough which may produce phlegm, fatigue, fever, sweating and shaking chills, chest pain when you breath or cough		√	

Frequency/Side effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Severe allergic reactions: sudden wheeziness, drop in blood pressure, and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat			√
Skin problems: Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS), Erythema multiforme (severe skin reactions): redness, blistering and/or peeling of large areas of the skin, raised red or purple skin patches, possibly with blister or crust in the center; possibly swollen lips, mild itching or burning			√
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			√
Unknown			
Musculoskeletal problems: muscle pain, tenderness (soreness when the muscle is pressed) or muscle weakness with or without fever		√	
Peripheral neuropathy (nerve damage): weakness, numbness and pain, usually in the hands and feet			√
Colitis (inflammation of colon): abdominal pain, bloody stools, diarrhea, fever, rectal pain, bloating, weight loss		√	
Shortness of breath, fatigue, dizziness, chest pain		√	

Frequency/Side effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Skin ulcer: round, open sore in the skin through which the underlying tissues can be seen			√
Pulmonary nodule (small, abnormal spots or masses in the lungs): Cough with phlegm/mucus or blood, and can lead to a collapsed lung (pneumothorax). Symptoms of a pneumothorax are shortness of breath, chest pain on one side, cough, fast breathing and heart rate, tiredness			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 15°C to 30°C, in a dry place. Protect from light. Keep out of reach and sight of children.

If you want more information about APO-LEFLUNOMIDE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-

products/drug-product-database.html); the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Date of Authorization: 2026-05-15