

# DATA SHEET

## AFT-Leflunomide

Leflunomide 10 mg and 20 mg tablets

### Presentation

AFT-LEFLUNOMIDE 10 mg tablets are round, white, film-coated tablets embossed with a "P" logo on one side and "10" on the other side.

AFT-LEFLUNOMIDE 20 mg tablets are triangular, off-white, film-coated tablets embossed with a "P" logo on one side and "20" on the other side.

### Uses

#### **Actions**

Leflunomide is an isoxazole derivative, immunomodulatory agent with a proven antiproliferative effectiveness. It inhibits dihydroorotate dehydrogenase, an enzyme involved in de novo pyrimidine synthesis. Additionally, several experimental models (both *in vivo* and *in vitro*) have demonstrated that leflunomide has an anti-inflammatory effect.

In animal models it was found that leflunomide extends the rejection time or reversed rejection reactions pertaining to chronic graft versus host disease and solid organ graft rejection.

In experimental septicaemia studies it was found that leflunomide had no impact in terms of altering the resistance of mice to bacterial pathogens.

#### **Pharmacokinetics**

##### **Absorption**

Following oral administration, leflunomide is quickly and almost entirely metabolised by first-pass metabolism to teriflunomide which is responsible for essentially all of the drug's activity *in vivo*. Only teriflunomide was detected in plasma samples taken four hours following oral administration of leflunomide.

No absolute bioavailability study has been undertaken in humans, however the bioavailability of teriflunomide in animals ranged from 76% in dogs to more than 90% in mice.

Peak levels of teriflunomide in plasma occurred between 6 to 12 hours post leflunomide dose. Given that the approximate half-life of teriflunomide is approximately 2 week, a loading dose of 100 mg leflunomide for three days is required to achieve a quick steady-state levels of teriflunomide. Without a loading dose it is estimated that achieving steady-state plasma concentrations would take approximately 2 months.

The multiple dosing studies in patients with rheumatoid arthritis show that pharmacokinetics parameters during the loading dose stage (100 mg daily for 3 days) and during daily maintenance doses (5 to 25 mg) are linear. These studies showed that clinical effect was closely related to teriflunomide plasma concentration and to the daily dose of leflunomide. Age, sex and body size only had a minimal, clinically irrelevant influence on inter-individual variability in terms of teriflunomide clearance.

In comparison to an oral solution the bioavailability of leflunomide from tablet is 80% . Food has not been found to affect the bioavailability of leflunomide.

### **Distribution**

Teriflunomide is extensively bound to albumin (>99%). The unbound fraction of teriflunomide in healthy volunteers was 0.62% Teriflunomide binding was found to be linear to up to 573 µg/mL. Binding of teriflunomide is marginally lower and more variable in patients suffering from rheumatoid arthritis or chronic renal insufficiency where the unbound fraction increased to 0.80% and 1.44% in these two patient groups respectively.

Teriflunomide has low apparent volume of distribution (approximately 11 L) which is consistent with the data indication extensive protein binding,.

The average teriflunomide plasma concentration at steady state for a 20 mg/day dose is approximately 30 µg/mL.

### **Metabolism**

Leflunomide is metabolised to one primary metabolite (teriflunomide) as well as to numerous minor metabolites. Metabolic transformation of teriflunomide is not controlled by a specific enzyme and has been found to occur in cytosolic and microsomal cellular fractions. The specific site of leflunomide metabolism not currently known. In vivo and in vitro studies indicate that both the GI wall and the liver are involved in the metabolism.

The use of radiolabelled (<sup>14</sup>C)-leflunomide in healthy volunteers show that no unchanged leflunomide can be detected in plasma, urine or faeces. Teriflunomide was the only radiolabelled metabolite detected in plasma and no preferential uptake by erythrocytes was found.

The metabolite 4-trifluoromethylaniline (TFMA) was found in both man and animal plasma but only in minimal amounts compared with teriflunomide (approximately 1000-fold less) and sometimes the concentrations were even below the limits of quantification of the test method. Concentrations in humans were typically <10 ng/mL and the maximum values recorded were in the region of 20 ng/mL.

### **Elimination**

Teriflunomide is removed from the body by metabolism and renal excretion of metabolites as well as direct biliary excretion. A study involving radiolabelled leflunomide showed that the excretion is slow. 89% to 94% of total radioactivity was excreted within 28 days. Approximately 43% of the total radioactivity was excreted through urine and 48% was through the faeces. It was found that the principal urinary metabolites were glucuronides derived from leflunomide (mainly in 0 - 24 hour samples) and an oxanilic acid derivative of teriflunomide. The main faecal component was teriflunomide.

The *in vivo* plasma half-life of teriflunomide was reduced from more than one week to about one day when activated charcoal or cholestyramine was used to assist the elimination (see

*Overdosage*). This indicates that biliary recycling is a significant contributor to teriflunomide's long elimination half-life. Studies in haemodialysis and chronic ambulatory peritoneal dialysis (CAPD) patients show that teriflunomide is not dialyzable.

Following intravenous administration of teriflunomide clearance averaged out at 31 mL/hr with an elimination half-life of 10 days.

### **Paediatric Pharmacokinetics**

The pharmacokinetics of teriflunomide after oral administration of leflunomide was assessed in 73 paediatric patients suffering from polyarticular course Juvenile Rheumatoid Arthritis (JRA). Patients were from 3 to 17 years of age. Population pharmacokinetic analysis has shown that paediatric patients with a body weight of  $\leq 40$  kg have a reduced clearance of teriflunomide when compared with adult rheumatoid arthritis patients.

### **Special Populations**

Gender The pharmacokinetics of leflunomide and teriflunomide is not gender dependant.

Age causes a change in the *in vivo* pharmacokinetics of leflunomide and teriflunomide (see '*Paediatric Pharmacokinetics*' above). Data for patients older than 65 years is limited.

Smoking Although data shows that smokers have a 38% increase in clearance compared with non-smokers, in terms of clinical efficacy no difference was found when comparing smokers and non-smokers.

Chronic Renal Impairment Single-dose studies in patients, with chronic renal impairment requiring either chronic ambulatory peritoneal dialysis (CAPD) or haemodialysis, showed that neither had a significant influence on teriflunomide plasma levels. The free fraction of teriflunomide increased by almost 100% but the mechanism of this increase is not known. Given that the kidneys have a role in drug elimination, and in the absence of comprehensive studies of leflunomide use in patients with renal impairment, caution should be exercised if leflunomide is administered to such patients.

Hepatic Impairment Given that teriflunomide is highly protein bound and given that it is cleared by hepatic metabolism and biliary secretion, and because of the risk of hepatotoxicity, leflunomide is contra-indicated in patients with impaired liver function.

### **Indications**

AFT-LEFLUNOMIDE is indicated for treating rheumatoid arthritis, for improving signs and symptoms of the disease, for retarding joint destruction and also for improving functionality and the quality of life. AFT-LEFLUNOMIDE can be used with patients who have not responded to alternative treatments or as a first line treatment in patients who have a contraindication to other medicines.

## **Dosage and Administration**

### **Loading Dose**

It is recommended that leflunomide therapy commences with a loading dose of 100 mg one time daily for three days. Not starting the therapy with a loading dose can decrease the risk

of adverse reactions if leflunomide is used with methotrexate. This may be important for patients who have a high risk of haematologic or hepatic toxicity, for example patients receiving concomitant treatment with methotrexate or other immunosuppressive agents or on similar medications (see *Warnings and Precautions*, "*Concomitant Use with Hepatotoxic and Haematotoxic Agents*" and "*hepatotoxicity*").

### **Maintenance Dose**

The recommended maintenance dose for rheumatoid arthritis is 20 mg leflunomide once a day. Doses of more than 20 mg/day are not recommended. Should dosing at 20 mg/day not be well tolerated then it can be decreased to 10 mg a day.

Liver enzymes and haematological criteria need to be monitored and dose adjusted or therapy discontinued if necessary.(see *Warnings and Precautions*). In light of the prolonged half-life of leflunomide's active metabolite, patients should be monitored after dose reduction because it could take several weeks for metabolite levels to reduce.

AFT-LEFLUNOMIDE tablets should be swallowed whole with adequate amount of liquid. The absorption of leflunomide is not affected by taking it with food. The tablets must NOT be divided.

Improvement of the patient's rheumatoid condition may begin as early as 4 weeks after commencing therapy. However there can be additional improvement after 4 to 6 months of continued treatment.

Currently there is insufficient experience available to enable dosage recommendations for patients who have a serum creatinine level of >133 µmoles/L (1.5 mg/dL).

Dosage adjustment for the elderly is not required.

### **Compatibility with other antirheumatic drugs**

If a patient is currently taking NSAIDs and/or low dose corticosteroids then these can be continued after starting leflunomide.

For information about co-administration with methotrexate and alternative hepatotoxic and haematotoxic drugs please refer to the Interactions section.

### **Contraindications**

AFT-LEFLUNOMIDE must not be given to:

- patients who have hypersensitivity to leflunomide or to any of the other tablet ingredients (see *Further Information*);
- patients who have severe immunodeficiency conditions, such as. AIDS;
- patients who have markedly impaired bone marrow function or marked anaemia, leukopenia or thrombocytopenia resulting from causes other than rheumatoid arthritis;
- patients who have uncontrolled severe infections;
- patients who have impaired liver function;
- women who are pregnant;

- women who are able to bear children and who are not using reliable contraception while taking AFT-LEFLUNOMIDE and for a sufficient period of time thereafter, so long as plasma levels of teriflunomide (the active metabolite) are over 0.02 mg/L, except when undergoing washout treatment (*see Use in Pregnancy*)
- women who are breast-feeding
- patients who have severe hypoproteinaemia
- patients with, or who have had, Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme

## Warnings and Precautions

### ***Concomitant use with Hepatotoxic and Haematotoxic Agents***

Increased side effects can result when leflunomide is taken concomitantly with hepatotoxic or haematotoxic medicines or when leflunomide therapy is followed by such medicines without a washout period. The chance of additive risks of side effects may continue for a significant period after changing treatments. In light of this the commencement of leflunomide treatment needs to be carefully considered - given these benefit/risk aspects. (*see Interactions*).

Pancytopenia is an uncommon event, but has been reported with leflunomide, with fatality in isolated cases. Such events have been reported most often in situations of recent, concomitant or subsequent use of potentially myelotoxic/haematotoxic agents, for example methotrexate (the rate of pancytopenia associated with methotrexate alone is reported in medical literature to be from 0.6% to 2.1%). If a patient displays evidence of pancytopenia on routine haematological monitoring, cease leflunomide, begin washout procedure and maintain close haematological monitoring until resolution is confirmed (*see Overdosage*).

Concomitant treatment with methotrexate and/or other hepatotoxic medicines may increase the risk of serious hepatic reactions. In order to reduce the risk of serious adverse reactions it is crucial that all monitoring recommendations are followed.

In light of the long half-life of teriflunomide (typically 1 to 4 weeks), adverse reactions may eventuate or remain even after administration of leflunomide has ceased (*see Adverse Effects*). In the event of a severe adverse reaction to leflunomide, or if teriflunomide needs to be cleared from the body quickly, then cholestyramine or charcoal has to be initiated as described in the Overdosage section hereof and continued or repeated as necessary. In the case of suspected severe immunological/allergic reactions, prolonged cholestyramine or charcoal administration may be needed to achieve rapid and sufficient clearance.

Washout procedures need to be performed when serious effects occur (for example hepatotoxicity, haematotoxicity or allergic reactions), in the case of desired or unintended pregnancy and if for any reason teriflunomide needs to be cleared from the body quickly.

### ***Haematological Monitoring***

A full blood cell count (including differential white blood cells and platelets count) should be conducted for all patients before commencing leflunomide treatment, and on a monthly basis for the initial 6 months, followed by 6-8 weeks checks afterwards. Monitoring should be continued on a monthly basis if leflunomide is used concomitantly with methotrexate, and/or other potential immunosuppressives. Patients with pre-existing anaemia, leukopenia and/or thrombocytopenia, and patients with impaired bone marrow

function or those at risk of bone marrow suppression, are at increased risk of haematological reactions.

### ***Hepatotoxicity***

Clinical trials involving leflunomide indicate that it can elevate liver function values, mainly ALT (SGPT) and AST (SGOT). Such effects were generally reversible.

Most transaminase increases were mild ( $\leq 2$  x the upper limit of normal (ULN) and were normally resolved while maintaining treatment. Significant elevations ( $> 2$  and  $\geq 3$  x ULN) were less common and were normally asymptomatic and reversible with reduced dosing or, if they persisted, then on discontinuing leflunomide treatment.

More significant elevations ( $> 3$  x ULN) occurred only rarely and were normally reversed by reducing the dose. Persistent elevations were resolved by discontinuing treatment with leflunomide. Overall, persistent elevations were not common after reducing the dose and were normally associated with concomitant use of a NSAID. Biopsy data did not show any association between leflunomide and the development of cirrhosis or hepatic fibrosis.

In rare cases severe liver damage, with fatality in isolated cases, have been reported during leflunomide treatment. Most such cases occurred during the initial 6 months of treatment. While confounding factors were present in many cases, a causal relationship to leflunomide could not be ruled out. It is considered crucial that monitoring recommendations are followed strictly (*see Liver function monitoring*).

### ***Liver Function Monitoring***

AST and ALT need to be checked before commencing leflunomide therapy and monitored at monthly or at even more frequent intervals for at least the initial 6 months and every 6-8 weeks thereafter if stability is attained. If leflunomide and methotrexate are administered concomitantly, AST, ALT and serum albumin testing need to be performed at monthly intervals.

In the case of confirmed AST or ALT increases between 2- and 3-fold the ULN, a reduction in dose may enable continued leflunomide administration under close monitoring.

In the case of minor elevations in AST or ALT ( $< 2$ -fold ULN), test should be repeated in 2-4 weeks.

In the case of moderate elevations in ALT or AST ( $> 2$ -fold but  $< 3$ -fold ULN), patients should be monitored carefully, with liver function tests performed each 2-4 weeks and dose reduced, if necessary.

If ALT or AST elevations of 2- to 3-fold ULN persist or if ALT or AST increases of more than 3-fold ULN are found, leflunomide treatment should be stopped. To rapidly lower leflunomide levels cholestyramine or activated charcoal should be administered, with close monitoring and further treatment with cholestyramine or activated charcoal as indicated.

### ***Patients with Renal Impairment***

After a single dose (100 mg) of leflunomide administered orally to 3 haemodialysis patients and also to 3 patients on continuous peritoneal dialysis (CAPD), the pharmacokinetics of

teriflunomide in CAPD subjects was found to be similar to that of healthy volunteers. A quicker elimination of teriflunomide was observed in subjects on haemodialysis and this was not due to extraction of drug in the dialysate but due to displacement of leflunomide from protein binding site. Caution should be exercised if leflunomide is given to patients with renal impairment (see *'Special Populations'*).

### ***Infections***

Medications with immunosuppressive properties have been known to cause patients to be more prone to infections, including opportunistic infections.. Infections may require vigorous treatment from an early stage. If severe uncontrolled infections eventuate it may be necessary to cease leflunomide treatment and administer cholestyramine (see *Overdosage*).

### ***Respiratory***

Interstitial lung disease has only rarely been reported during leflunomide treatment (see *Adverse Effects*). Interstitial lung disease can be a potentially fatal disorder and it can occur acutely during therapy. Cough and dyspnoea, or other pulmonary symptoms, with or without fever may indicate the need for further investigation. Discontinuation of the therapy and implementation of a washout with cholestyramine (see *OVERDOSAGE*) may be appropriate. 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 to worsen during therapy.

Interstitial lung disease presenting acutely (interstitial pneumonitis) may occur more frequently with concomitant methotrexate.

### ***Immunosuppression***

While there is no clinical history due to the potential for immunosuppression leflunomide is not recommended for patients who have bone marrow dysplasia, severe immunodeficiency, or severe uncontrolled infections.

If a serious infection occurs, it may be necessary to stop leflunomide therapy and administer cholestyramine or charcoal (see *Overdosage*). Severe infections including sepsis, which may be fatal, have been reported in patients receiving leflunomide but only on rare occasions. Most such reports were confounded by concomitant immunosuppressant therapy and/or by comorbid illness which, in addition to rheumatoid disease, may give patients a predisposition to infection.

There have been rare reports of pancytopenia, very rare reports of agranulocytosis and rare reports of thrombocytopenia in patients taking leflunomide (see *Warnings and Precautions "Concomitant use with hepatotoxic and haemotoxic agents including methotrexate"*). In most such cases patients received concomitant therapy with methotrexate or other immunosuppressives or they had recently stopped such therapies. Some cases involved a history of significant haematologic abnormality. Leflunomide should be administered with caution and with regular haematologic monitoring in these patients (see *Haematological Monitoring*). Combination therapy with leflunomide and methotrexate has not been studied adequately.

If bone marrow suppression is seen in a patient taking leflunomide then the treatment should cease and cholestyramine or charcoal administered to reduce the leflunomide plasma concentration. (see *Overdosage*).

Hematologic toxicity should be monitored when patients are switched from leflunomide to another anti-rheumatic agent with a known potential for haematologic suppression, This is because there will be overlap of systemic exposure to both compounds. The risk may be reduced by administration of cholestyramine or charcoal, but this may cause the disease to worsen if the patient had been responding to the treatment with leflunomide.

A delay in the healing of accidental cornea lesions was found in dogs treated with leflunomide. This may be due to leflunomide's immunosuppressive effect. However the clinical relevance of this is unclear.

Patients who have tuberculin reactivity need to be carefully monitored due to the risk of tuberculosis reactivation.

### ***Wash-out procedure for Severe Adverse Reactions***

In light of the long half-life of teriflunomide (typically 1 to 4 weeks), adverse reactions may eventuate or remain even after administration of leflunomide has ceased (see *Adverse Effects* ). In the event of a severe adverse reaction to leflunomide, or if teriflunomide needs to be cleared from the body quickly, then cholestyramine or charcoal has to be initiated as described in the *Overdosage* section hereof and continued or repeated as necessary. In the case of suspected severe immunological/allergic reactions, prolonged cholestyramine or charcoal administration may be needed to achieve rapid and sufficient clearance.

Washout procedures need to be performed when serious effects occur (for example hepatotoxicity, haematotoxicity or allergic reactions), in the case of desired or unintended pregnancy and if for any reason teriflunomide needs to be cleared from the body quickly.

### ***Antigenicity***

Leflunomide was not found to be antigenic in the active systemic and passive cutaneous anaphylaxis test in guinea pigs and was found to be without sensitising properties.

### ***Carcinogenicity, Mutagenicity, and Impairment of Fertility***

Leflunomide (teriflunomide) was not found to be mutagenic in bacteria (*Salmonella typhimurium* and *Escherichia coli*) or Chinese hamster ovary cells. It did not cause chromosomal damage *in vivo* (mouse and Chinese hamster bone marrow cells), and was not found to induce unscheduled synthesis of DNA *in vitro* in mammalian cells. Trifluoromethylaniline, which is a minor metabolite of leflunomide, was found to be mutagenic and caused chromosomal damage in *in vitro* assays. However it did not cause chromosomal damage *in vivo* (Chinese hamster bone marrow cells) at levels greater than those anticipated in humans.

A carcinogenicity study in mice taking leflunomide orally for two years showed an increased rate of malignant lymphoma in males receiving 15 mg/kg/day leflunomide [associated with plasma teriflunomide concentrations (AUC) comparable to that anticipated in humans], an increase in bronchioalveolar adenomas in males receiving  $\geq 5$  mg/kg/day (teriflunomide AUC comparable to or approximately 50% less than that anticipated in humans) and an increase

in bronchioalveolar adenomas and carcinomas in females receiving 1.5 mg/kg/day (teriflunomide AUC at least 10-20 times less than that anticipated in humans). The increase in malignant lymphoma development was more than likely due to leflunomide's immunosuppressant effects. A no-effect dose or AUC for the development of lung tumours in female mice was not found, however the relevance of these results to humans is unclear. Leflunomide did not display carcinogenicity in rats when given orally in doses up to 6 mg/kg/day (associated with teriflunomide AUC 25-65 times less than expected for humans).

As leflunomide also has potential for immunosuppression, the risk of malignancy, particularly lymphoproliferative disorders, is increased when leflunomide is used in combination with some immunosuppression medications. No apparent increase in the incidence of malignancies and lymphoproliferative disorders was reported in clinical trials involving leflunomide, however additional studies would be necessary to determine whether leflunomide presents an increased risk of malignancy or lymphoproliferative disorders.

### **Effects on Fertility**

The oral administration of leflunomide at doses up to 4 mg/kg/day plasma [teriflunomide concentrations (AUC) about 10-25 times lower than that expected in humans] did not show any effect on fertility in rats. However reduced spermatogenesis has been found in mice, rats and dogs given oral leflunomide at greater doses or over longer periods of time (plasma teriflunomide AUC similar to or significantly lower than expected for humans).

### **Use in Pregnancy (Category X)**

Because teriflunomide is teratogenic in rabbits and rats it may cause foetal damage in humans. Leflunomide must not be given to pregnant women, or women of childbearing potential who are not using reliable contraception while taking leflunomide and for a sufficient period of time afterwards (for waiting period or abbreviated wash-out period please see below). Pregnancy needs to be ruled out before commencing treatment with leflunomide.

Women of childbearing potential should only receive leflunomide after confirmation that they are using a reliable contraceptive. A study involving leflunomide given to healthy females concomitantly with a triphasic oral contraceptive pill containing 30 µg ethinyloestradiol showed that there was no reduction in the contraceptive activity of the pill, and teriflunomide pharmacokinetics parameters were at anticipated levels.

Female patients need to be told that if there is a delay in the onset of period or if there is another reason to suspect pregnancy then they need to notify their physician immediately and test for pregnancy. Should the test be positive then the physician and patient need to discuss the risk to the foetus. Rapidly lowering the blood level of the active metabolite using the drug elimination procedure described herein, may decrease the risk to the foetus.

One of the wash-out procedures listed below is recommended for women who have been taking leflunomide and who may become pregnant, The same wash-out procedures are also recommended prior to conception after stopping leflunomide treatment:

- cholestyramine 8 g administered 3 times each day for 11 days or alternatively
- 50 g activated charcoal administered 4 times each day for 11 days.

The 11 days do not have to be consecutive unless there is need to quickly reduce the level of teriflunomide in plasma. Both cholestyramine and activated charcoal can impact on absorption of estrogens and progestrogens to the extent that reliable oral contraception cannot be guaranteed during the washout procedure. During this period it is recommended that a suitable alternative contraceptive method be used.

### **Use in Lactation**

Some animal studies suggest that leflunomide or its metabolites pass into breast milk. Women must not breast feed while taking leflunomide.

### ***Effects on Ability to Drive and Use Machines***

Leflunomide may cause dizziness and drowsiness. It is therefore advisable to exercise caution when driving, operating machinery, or engaging in other potentially hazardous activities.

### **Plasma Monitoring**

When the wash-out has been performed, plasma levels of teriflunomide less than 0.02 mg/L need to be verified by two separate tests performed at least two weeks apart. Based on the data currently available plasma levels of teriflunomide of less than 0.02 mg/L are expected to present only minimal risk. Without washout procedure it may take up to 2 years to get to teriflunomide levels of less than 0.02 mg/L (after ceasing treatment with leflunomide), due to the individual variation in drug clearance.

### ***Blood Pressure Monitoring***

The patient's blood pressure should be checked before commencing leflunomide treatment and then periodically afterwards.

### ***Use in Males***

Based on information available there is no suggestion that leflunomide is associated with an increased risk of male-mediated foetal toxicity. Animal studies to assess this risk have not been conducted. In order to reduce any risk, men who want to father a child should consider ceasing use of leflunomide and perform washout procedure.

### ***Use in Children***

Leflunomide is not recommended for use in children and adolescents of less than 18 years of age because its safety and efficacy have not been studied for that age group.

### ***Use in the Elderly***

Safety and efficacy in patients over 75 years of age have not been studied. Leflunomide should be used cautiously in this age group

### ***Skin reactions***

Administration should be discontinued in the event of ulcerative stomatitis.

There have been very rare reports of Stevens Johnson syndrome or toxic epidermal necrolysis for patients treated with leflunomide. Use of leflunomide and any other associated medication must stop as soon as skin and/or mucosal reactions which raise the suspicion of such severe reactions are observed. In such cases cholestyramine or charcoal should be used immediately to bring down the plasma concentration of leflunomide (see *Overdosage*). A complete washout is crucial and in such cases re-exposure to leflunomide is contraindicated.

## Adverse Effects

Adverse reactions which were reported during the post-marketing period are listed below: These are classified according to body system categories using the following as definitions:

Common  $\geq 1/100$  and  $< 1/10$   
Uncommon  $\geq 1/1000$  and  $< 1/100$   
Rare  $\geq 1/10000$  and  $< 1/1000$   
Very rare  $< 1/10000$

### ALLERGIC REACTIONS, SKIN AND APPENDAGES

Common	Mild allergic reactions (including maculopapular and other rashes), pruritis, eczema, dry skin, increased hair loss
Uncommon	Urticaria
Very rare:	Severe anaphylactoid reactions. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme. In reports received to date a causal relationship with leflunomide treatment was not established however it cannot be ruled out.

Vasculitis, including cutaneous necrotising vasculitis. In light of underlying disease a causal relationship could not be determined

### HAEMIC AND LYMPHATIC SYSTEM

Uncommon:	thrombocytopenia with platelet count $<100 \times 10^9/L$ ( $<100G/L$ )
Rare:	eosinophilia, leukopenia (leukocytes $<2 G/l$ ), pancytopenia,
Very rare:	agranulocytosis

### LIVER

Rare:	Hepatitis, jaundice/cholestatis
Very rare:	Severe liver injury such as hepatic failure, and acute hepatic necrosis, that may be fatal, pancreatitis.

### INFECTION

Rare:	Severe infections, which includes opportunistic infections, and sepsis, which may be fatal. (The majority of case reports were confounded by concomitant immunosuppressant therapy and/or comorbid illness, as well as rheumatoid disease, which may give patients a predisposition to infection).
-------	--

### CARDIOVASCULAR

Common: increase in blood pressure .  
Very rare: vasculitis (In light of the underlying disease a causal relationship could not be determined)

#### RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

Rare: Interstitial lung disease (including interstitial pneumonitis), which can be fatal.

#### NERVOUS SYSTEM

Common: headache, dizziness, paresthesia  
Uncommon: Taste disturbances, anxiety.  
Very rare: Peripheral neuropathy

#### OTHER

Common: Weight loss, asthenia, diarrhoea

Concomitant or consecutive use of potentially myelotoxic agents, taken recently, might be associated with a greater risk of haematological effects.

Very rare instances of severe liver damage, with fatality in isolated cases, have been reported during leflunomide treatment. This risk may increase if leflunomide is combined with other disease-modifying antirheumatic drugs. The majority of such cases occurred during the initial 6 months of treatment. While confounding factors were present in many cases, a causal connection to leflunomide cannot be ruled out. It is considered crucial that monitoring recommendations are followed strictly.

## Interactions

The enzymes responsible for metabolising leflunomide and its metabolites are not well known or understood. *In vitro* studies suggest that teriflunomide suppresses cytochrome P4502C9 (CYP2C9). It is recommended that caution be exercised when leflunomide is administered with other drugs, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin and tolbutamide (see below). The extensive protein binding ability of teriflunomide may result in displacement of other highly-bound medicines.

### ***Cimetidine***

Lack of any significant interaction has been demonstrated in an *in vivo* interaction study with cimetidine (non-specific cytochrome P450 inhibitor).

### ***Rifampicin***

It has been found that after concomitant administration of one dose of leflunomide to subjects receiving multiple doses of rifampicin (non-specific cytochrome P450 inducer) peak levels of teriflunomide were increased by approximately 40%, whereas the AUC did not change to any significant degree. The associated mechanism is unclear. In light of the potential for teriflunomide levels to increase continually with multiple dosing, caution needs to be exercised for patients taking both leflunomide and rifampicin.

## **Warfarin**

There have been rare reports of prothrombin time increase when leflunomide and warfarin were co-administered. *In vitro* plasma protein binding interaction studies with warfarin at clinically relevant concentrations did not show an interaction. This does not rule out the possibility of an interaction by other means, for example inhibition of drug metabolism. However this was not the subject of the studies.

## **NSAIDs**

NSAIDs (including COX-2 inhibitors) are known to cause hepatotoxicity. In view of this caution is recommended when using leflunomide concomitantly (see *Warnings and Precautions*). Some studies indicate that teriflunomide can displace ibuprofen and diclofenac and increase their unbound fraction in plasma by 10% to 50%. No safety problems were observed in clinical trials when leflunomide and NSAIDs metabolised by CYP2C9 were co-administered.

## **Tolbutamide**

*In vitro* studies have shown that teriflunomide at concentrations corresponding to the clinical range can cause increases ranging from 13% to 50% of the free fraction of tolbutamide. The significance of this finding from a clinical perspective is not known. The unbound fraction of teriflunomide was found to increase 2-3 fold in the presence of tolbutamide.

## **Methotrexate**

There is evidence from spontaneous reporting and prescribing data that interstitial pneumonitis may occur more frequently with concomitant methotrexate.

A small study involving leflunomide (10-20 mg/day) coadministered with methotrexate (10-25 mg/week) showed that coadministration increases the risk of hepatotoxicity. No pharmacokinetic interaction was found.

An increase in liver enzymes (more than 3-fold) was noted in 5 patients. All of these increases were resolved, two with continuation of both drugs and three after stopping leflunomide.

A 2- to 3-fold increase was noted in five additional patients. All elevations resolved, two with continuation of both drugs and three after stopping leflunomide. Three patients met ACR criteria for liver biopsy (1: Roegnik Grade I, 2: Roegnik Grade IIIa). (see *Warnings and Precautions*, "*Concomitant Use with Hepatotoxic and Haematotoxic Agents*" and "*Hepatotoxicity*").

## **Hepatotoxic and Haematotoxic Drugs**

Increased side effects can result when leflunomide is taken concomitantly with hepatotoxic or haematotoxic medicines or when leflunomide therapy is followed by such medicines without

a washout period. The chance of additive risks of side effects may continue for a significant period after changing treatments. In light of this the commencement of leflunomide treatment needs to be carefully considered - given these benefit/risk aspects.

Because of the risk of additive hepatotoxic effects it is recommended that patients avoid excessive alcohol consumption while taking leflunomide.

### ***Oral Contraceptives***

No effect on the anti-ovulatory function of the contraceptive or the pharmacokinetics of teriflunomide was observed when leflunomide was taken concomitantly with a low-dose oral contraceptive by healthy females

### ***Vaccinations***

Clinical data pertaining to the efficacy and safety of vaccinations while under leflunomide treatment is not available. Vaccination using live vaccines is not recommended. A live vaccine should only be given following a period of at least 6 months after stopping leflunomide treatment.

### ***Cholestyramine and Activated Charcoal***

It is recommended that patients taking leflunomide not be treated with cholestyramine or activated charcoal as this leads to a rapid and significant decrease in teriflunomide plasma levels.. The mechanism is believed to involve interruption of enterohepatic recycling and/or gastrointestinal dialysis of teriflunomide.

### **Overdosage**

There have been reports of acute and chronic overdose in patients taking leflunomide at up to five times the recommended daily dose with no adverse events reported for the majority of cases. Adverse events were in line with leflunomide's safety profile. The most frequent adverse events were elevated liver function tests, leukopenia, diarrhoea, abdominal pain and anaemia.

### ***Management***

It is recommended that cholestyramine or charcoal are administered in the case of a significant overdose or toxicity. Cholestyramine administered orally at a dose of 8 g three times daily for 24 hours has been found to reduce plasma levels of teriflunomide by approximately 40% in 24 hours, and by 49-65% in 48 hours in healthy volunteers.

Administration of activated charcoal suspension orally or via nasogastric tube (50 g every 6 hours for 24 hours) has been found to reduce plasma concentrations of teriflunomide by 37% within 24 hours and by 48% within 48 hours.

Wash-out procedures can be repeated if necessary.

Studies involving haemodialysis and CAPD patients have shown that teriflunomide is not dialyzable.

## **Pharmaceutical Precautions**

Store below 25 °C in a dry place, protect from light.

## **Medicine Classification**

Prescription only medicine

## **Package Quantities**

AFT-LEFLUNOMIDE 10 mg and 20 mg tablets are available in bottles of 30 and 100 tablets.

## **Further Information**

Each tablet contains leflunomide, polyethylene glycol, maize starch, lactose, silicon dioxide, povidone, crospovidone, polyvinyl alcohol, talc and titanium dioxide. The 20 mg tablets also contain iron oxide yellow.

The consent to distribute AFT-LEFLUNOMIDE tablets is valid for 2 (two) years from 17 July 2008.

## **Name and Address**

AFT Pharmaceuticals Ltd  
P O Box 33-203  
Takapuna  
AUCKLAND

Telephone: (09) 488-0232  
Facsimile: (09) 488-0234

## **Date of Preparation**

4<sup>th</sup> February 2011