1. NAME OF THE MEDICINAL PRODUCT

BAGEDA 20 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Each film-coated tablet contains 20 mg Leflunomide as active substance.

Excipients:

Lactose monohydrate	67.0000 mg
Lactose anhydrous	52.2000 mg
Sodium starch glycolate	15.0000 mg
Sunset yellow FCF (E110)	0.0036 mg
Tartrazine (E102)	0.0280 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Light yellow colored, round, plain on both sides, biconvex coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BAGEDA is indicated for treatment of adult patients with:

1. Active rheumatoid arthritis to improve physical function,
2. Active psoriatic arthritis

Regarding the use of BAGEDA in patients recently pre-treated with DMARDs (disease modifying antirheumatic drug) which are toxic for the liver (hepatotoxic) or for the blood (haematotoxic) and

patients for whom substitution with another DMARD is planned, see "Special warnings and precautions for use".
Switching from leflunomide to another DMARD without following the elimination procedure may also increase risk of serious adverse reactions even for a long time after switching.

4.2 Posology and method of administration

This product should be prescribed by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis. Special monitoring measures must be followed before initiation and during course of treatment (See "Monitoring Requirement").

Posology/frequency and duration of administration:

- In rheumatoid arthritis: BAGEDA therapy is usually started with a loading dose of 100 mg once daily for 3 days. The recommended maintenance dose is leflunomide 10 mg to 20 mg once daily depending on the severity (activity) of the disease.
- In psoriatic arthritis: BAGEDA therapy is started with a loading dose of 100 mg once daily for 3 days. The recommended maintenance dose is leflunomide 20 mg once daily.

An improvement in the rheumatoid condition usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months. Treatment with non-steroidal anti-inflammatory drugs and/or corticosteroids may be continued when starting BAGEDA.

Method of administration:

BAGEDA film-coated tablets should be swallowed without chewing and with a sufficient amount of liquid (approximately 120ml). They may be taken with or without food.

Monitoring Requirement

Similar to other currently available medicines (e.g. methotrexate) for treatment of RA, patients on BAGEDA will need to do some blood test during BAGEDA treatment. This is to monitor their health conditions and to ensure that they are doing fine with the BAGEDA treatment.

ALT (SGPT), AST and complete blood cell count, including differential white blood cell count and platelets, must be performed before start of leflunomide treatment & during treatment period. The schedule of blood test for patients will be once every 2 weeks during the first 6 months of treatment. Subsequently, the frequency of the blood tests will be reduced to once in 2 months and thereafter.

Additional information relating to specific populations

Due to the prolonged half-life of the active metabolite of leflunomide, patients should be carefully observed after dose reduction, since it may take several weeks for metabolite levels to decline.

Renal failure

There is no dose adjustment recommended in patients with mild renal insufficiency.

Pediatric population

Leflunomide is not recommended for use in patients below 18 years since efficacy and safety in juvenile rheumatoid arthritis (JRA) have not been established (see Section 5.1 and 5.2).

Geriatric population

No dosage adjustment is required in patients above 65 years of age.

4.3 Contraindications

• Patients with hypersensitivity (especially previous Stevens- Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) to leflunomide, to the principal active metabolite teriflunomide or to any of the excipients (see Section 6.1).

• Severe immunodeficiency states, e.g. patients with AIDS.

• Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis.

• Patients with serious infections (see Section 4.4),

• Patients with moderate to severe renal insufficiency, because insufficient clinical experience is available in this patient group.
• Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome.

Hepatoxicity:
It is contra indicated in patients with impairment of liver function.
Pregnancy:
Pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with leflunomide and thereafter as long as the plasma levels of the active metabolite are above 0.02 mg/l (see section 4.6). Pregnancy must be excluded before starting of treatment with leflunomide (see section 4.6).

•Women in lactation period should not breast feed during leflunomide use (see Section 4.6).

4.4 Special warnings and precautions for use
Before initiating treatment with BAGEDA, careful consideration during the risk-benefit evaluation must be given to the possibility of increased side effects in patients recently pre-treating with hepatotoxic or haematotoxic DMARDs.
Treatment with BAGEDA requires careful medical supervision.

- General: serious side effects (e.g. hepatotoxicity, haematotoxicity or allergic reactions) may occur or persist (see "Undesirable effects") - given the long half-life of the active metabolite of leflunomide - even after treatment has been stopped. Therefore, when such effects occur, when any additive risks (i.e. kinetic interaction, organ toxicity) must be precluded, or when substitution with another DMARD (e.g. methotrexate) is planned, the following elimination procedure should be carried out: Administer cholestyramine (8 g three times daily) or alternatively, activated charcoal (powder made into a suspension, 50 g four times daily). The complete procedure usually takes 11 days, but may be modified depending on clinical or laboratory variables. For suspected

severe immunologic/allergic reactions, more prolonged cholestyramine or activated charcoal administration may be necessary to achieve rapid and sufficient elimination.

Co-administration of teriflunomide with leflunomide is not recommended as leflunomide is the parent compound of teriflunomide.

- Liver: Since the active metabolite of leflunomide is highly protein bound and cleared via hepatic metabolism and biliary secretion, plasma levels are expected to be increased in patients with hypoproteinemia. BAGEDA is contraindicated in patients with severe hypoproteinemia or liver impairment (see "Contraindications"). The use of leflunomide is not recommended in patients with evidence of infection with hepatitis B or C viruses.

For confirmed ALT elevation between 2and 3- fold the upper limit of normal, with a dose reduction from 20 to 10mg/day, administration of leflunomide may be continued under weekly monitoring. If nevertheless ALT elevations persist or if ALT elevations of more than 3-fold the upper limit of normal are present, leflunomide should be discontinued and the elimination procedure described above should be implemented.

Rare cases of serious liver injury, in isolated cases with fatal outcome, have been reported during treatment with leflunomide. Adherence to the above mentioned monitoring measure is essential to avoid serious liver damage (See "Undesirable effects").

AST and ALT as well as blood pressure must be checked before the start of leflunomide treatment and periodically thereafter. A complete blood cell count, including differential white blood cell and platelets, must be performed before start of and during leflunomide treatment (See "Monitoring Requirement").

- Blood formation and immune systems: the risk of haematological disorders (typically manifested, e.g., by paleness, tiredness, increased proneness to infections or bruising) increased in patients with pre-existing anaemia, leucopenia and/or thrombocytopenia, as well as in those with impaired bone marrow function or in those at risk of bone marrow suppression. The blood picture (complete blood cell count, including differential white blood cell count and platelet count) must be monitored frequently in these patients. (See "Monitoring Requirement") if such disorders

occur, the above- mentioned elimination procedure should be considered. In the event of severe haematological reactions, including pancytopenia, BAGEDA and any concomitant myelosuppressive medication must be discontinued and the elimination procedure initiated.

- Infections: medications like leflunomide that have immunosuppression potential may cause patients to be more susceptible to infections, including opportunistic infections. Infections may be more severe in nature (see "Undesirable effects"). and may therefore require early and vigorous treatment. In the event that a serious infection occurs it may be necessary to interrupt leflunomide treatment and administer the elimination procedure as described above.

Rare cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients receiving leflunomide among other immunosuppressants.

The risk of tuberculosis should be considered. Before starting treatment, all patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations. Patients with a history of tuberculosis should be carefully monitored because of the possibility of reactivation of the infection.

- Respiratory: interstitial lung disease has been reported rarely during treatment with leflunomide. The risk of its occurrence is increased in patients with a history of interstitial lung disease. Interstitial lung disease is a potentially fatal disorder, which may occur acutely during therapy. Pulmonary symptoms, such as cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation as appropriate.

- Peripheral Neuropathy: Cases of peripheral neuropathy have been reported in patients receiving leflunomide. Most patients improved after discontinuation of leflunomide. However there was a wide variability in final outcome, i.e. in some patients the neuropathy resolved and 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

leflunomide develops a peripheral neuropathy, consider discontinuing therapy and performing the drug elimination procedure (see “Special warnings and precautions for use”.

- Combination with other treatments: Combined use – in particular in long-term treatment – of BAGEDA with antimalarials used in rheumatic diseases (e.g. chloroquine and hydroxychloroquine) with gold salts (intramuscular or oral), or with D-penicillamine, azathioprine and other immunosuppressive medicines (including Tumour Necrosis Factor alpha-Inhibitors), has not been adequately studied up to now in randomized trials (with the exception of methotrexate, see “Interactions”). Since additive or even synergistic toxicity (e.g. hepatotoxicity of haematotoxicity) may occur, combination therapy with another DMARD (e.g. methotrexate) is not advisable.
- Skin and mucous membranes reactions: If ulcerative inflammations of the oral mucosa (ulcerative stomatitis) occur, BAGEDA should be discontinued.

Severe, sometimes life-threatening bullous skin and mucous membrane reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis and Drug Reaction with Eosinophilia and Systemic Symptoms) have been reported (see “Undesirable effects”). Once skin and/or mucosal changes (e.g. in the mouth) occur possibly indicating the development of such reactions, BAGEDA and any other associated medicine must be discontinued and the above-mentioned elimination procedure initiated immediately. Complete elimination is essential, and treatment with BAGEDA must not be resumed.

Pustular psoriasis and worsening of psoriasis have been reported after the use of leflunomide. Treatment withdrawal may be considered taking into account patient’s disease and past history.

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

- Driving: Some adverse effects, such as dizziness, may impair the ability to concentrate and react, and therefore, constitute a risk in situations where these abilities are of particular importance (e.g., operating a vehicle or machinery).
- Blood pressure must be checked before the start of leflunomide treatment and periodically thereafter.

Lactose

BAGEDA contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

BAGEDA does not contain sodium. This situaiton should be considered for patients with controlled sodium diet.

Sunset yellow FCF

BAGEDA contains 0.0036 mg sunset yellow FCF in each dose. Sunset yellow FCF may cause allergic reactions.

Tartrazine

BAGEDA contains 0.028 mg tartrazine in each dose. Tartrazine may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions studies have only been performed in adults.

- Recent or concomitant use of hepatotoxic or haematotoxic medicines – or immunosuppressive substances or the use of such following BAGEDA treatment without a washout period – may lead to increased side effects.

- Methotrexate: Increase in liver enzymes was reported in clinical studies with co-administration of leflunomide and methotrexate. Therefore, liver enzymes should be monitored closely in the initial phase after a changeover to methotrexate has been demonstrated.
- Vaccinations: Since no clinical data are available on the efficacy and safety of concomitant vaccinations, live vaccines should not be administered during treatment and - after discontinuation of BAGEDA - consideration should be given to the long half-life of leflunomide.
- Warfarin: There have been case reports of increased prothrombin time, when leflunomide and warfarin were co-administered. Close INR follow-up and monitoring is recommended when warfarin is co-administered with leflunomide.
- Alcohol should be avoided during treatment, since additive hepatotoxic effects may occur.
- Cholestyramine and activated charcoal rapidly and significantly reduce the plasma concentration of the active metabolite of leflunomide and, hence, the effectiveness of BAGEDA. Furthermore, either may also influence the absorption of oestrogens and progestagens and, hence, the efficacy of oral contraceptives (to be noted in this regard is the fact that the efficacy of triphasic oral contraceptives is not influenced by leflunomide itself). Alternative contraceptive measures should be substituted for the duration of the above-mentioned elimination procedure (see “Special warnings and precautions for use”).
- BAGEDA may influence the inactivation of certain other medicines metabolised by CYP2C9, an enzyme system of the liver. No safety problems, however, have been observed in combined use with medicines common in the treatment of rheumatoid arthritis (non-steroidal anti-inflammatory drugs, i.e. NSAIDs), whereas caution should be taken in combined use with other medicines metabolized by CYP2C9 (e.g., phenytoin, warfarin, tolbutamide, rifampicin).

Pharmacokinetic and pharmacodynamics interaction studies were conducted with the active metabolite of leflunomide (A771726). As similar drug-drug interactions cannot be excluded for leflunomide at recommended doses, the following recommendations should be considered in patients treated with leflunomide:

- Effect on CYP2C8 substrates: There was an increase in mean repaglinide Cmax and AUC (1.7- and 2.4-fold, respectively), following repeated doses of A771726, suggesting that A771726 is an inhibitor or 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.
- Effect on CYP1A2 substrates: Repeated doses of A771726 decreased Cmax and AUC of caffeine (CYP1A2 substrate) by 18% and 55% respectively, suggesting that A771726 may be a weak inhibitor of CYP1A2 in vivo. Therefore, medicinal products metabolised by CYP1A2 (such as duloxetine, alosetron, theophylline and tizanidine) should be used with caution during concomitant treatment, as it could lead to the reduction of the efficacy of these products.
- Effect on organic anion transporter 3 (OAT3) substrates: There was an increase in mean cefaclor Cmax 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 co-administered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution is recommended.
- Effect on BCRP and/or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates: There was an increase in mean rosuvastatin Cmax and AUC (2.65- and 2.51-fold, respectively), following repeated doses of A771726. However, there was no apparent impact of this increase in plasma rosuvastatin exposure on the HMG-CoA reductase activity. If used together, the dose of rosuvastatin 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, rifampicin) 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.

- Effect on oral contraceptive (0.03 mg ethinylestradiol and 0.15 mg levonorgestrel): There was an increase in mean ethinylestradiol Cmax and AUC0-24 (1.58- and 1.54-fold, respectively) and levonorgestrel Cmax and AUC0-24 (1.33- and 1.41-fold, respectively) following repeated doses of A177276. 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.
- Effect on warfarin: Repeated doses of A771726 had no effect on the pharmacokinetics of S-warfarin, indicating that A771726 is not an inhibitor or inducer of CYP2C9. However, a 25% decrease in peak international normalised ratio (INR) was observed when A771726 was co-administered with warfarin as compared with warfarin alone. Therefore, when warfarin is co-administered, close INR follow-up and monitoring is recommended.

4.6 Pregnancy and lactation

BAGEDA is contraindicated in pregnant women and pregnancy must be excluded before start of treatment.

In a small prospective study in women (n=64) who became inadvertently pregnant while taking leflunomide for no more than three weeks after conception and followed by a drug elimination procedure, no significant differences (p=0.13) were observed in the overall rate of major structural defects (5.4%) compared to either of the comparison groups (4.2% in the disease matched group [n=108] and 4.2% in healthy pregnant women [n=78]).

Lactation: Leflunomide or its metabolites may pass into breast milk. Breast-feeding women must, therefore, not receive BAGEDA. (see “Contraindications”).

Precautions and recommendations in conjunction with pregnancy and family planning

Based on available information, the risk of malformations in new-born infants of men taking BAGEDA cannot be excluded. Men should be aware of such a risk and should not take BAGEDA without using reliable contraceptive measures. To minimize any possible risk, men wishing to father a child should contact their doctor, who may advise that intake of BAGEDA be discontinued and the above-mentioned elimination procedure be carried out for 11 days.

In women, sufficient elimination of this metabolite from the body prior to pregnancy is essential to avoid the risk of malformation in the infant. Therefore, women wishing to become pregnant who are taking BAGEDA (or have taken it within the previous 2 years) must first speak with their doctor, who may advise – as a follow-on measure to the discontinuation of Bageda - either implementing the elimination procedure (for 11 days as in the case of men) or waiting until two full years have elapsed.

In both sexes, sufficient elimination of active metabolites should subsequently be confirmed by two separate blood laboratory tests, the first to be carried out after conclusion of the elimination procedure – or, alternatively in the case of women, 2 years after discontinuation – and the second at least 14 days later. If both test values of active metabolites are below 0.02mg/l in blood plasma, the risk of malformation is very low.

If there is any delay in onset of the period or any other reason to suspect pregnancy, the doctor must be notified immediately and pregnancy testing carried out. If positive, the risk to pregnancy must be discussed. Carrying out the elimination procedure at the first delay of the period may decrease the risk to the foetus from BAGEDA.

4.7 Effects on ability to drive and use machines

In the case of side effects such as dizziness the patient's ability to concentrate and to react properly may be impaired. In such cases patients should refrain from driving cars and using machines.

4.8 Undesirable effects

Classification of expected frequencies:

Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon: (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (<1/10,000); not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Cardiac disorders

Common: mild increase in blood pressure; Rare: severe increase in blood pressure Not known: pulmonary hypertension

Blood and lymphatic system disorders

Common: Leukopenia (leukocytes > 2 G/I);

Uncommon: Anaemia, mild thrombocytopenia (platelets < 100 G/I);

Rare: Pancytopenia (probably by antiproliferative mechanism), Leukopenia (leukocytes < 2G/I), eosinophilia;

Very rare: agranulocytosis.

Recent, concomitant or consecutive use of potentially myelotoxic agents may be associated with a higher risk of haematological effects.

Nervous system

Common: paraesthesiae, headache, dizziness; weakness, peripheral neuropathy

Respiratory, thoracic and mediastinal disorders

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

Gastrointestinal disorders

Common: diarrhea, nausea, vomiting, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain; colitis including microscopic colitis

Uncommon: taste disturbances;

Very rare: pancreatitis.

Renal and urinary disorders

Not known: Renal failure

Skin and subcutaneous tissue disorders

Common: increased hair loss, eczema, rash (including maculopapular rash), pruritus, dry skin;
Uncommon: urticaria
Very rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
Not known: cutaneous lupus erythematosus, pustular psoriasis or worsening psoriasis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), skin ulcer (see "Special warnings and precautions for use").
Musculoskeletal system and connective tissue disorders
Common: tenosynovitis;
Uncommon: tendon rupture
Metabolism and nutritional disorders
Common: CPK increased
Uncommon: hypokalaemia, hyperlipidemia, hypophosphataemia Rare: LDH increased;
Not known: hypouricemia
Infections and infestations
Rare: Severe infections and sepsis, which may be fatal
Like other agents with immunosuppressive potential, leflunomide may increase susceptibility to infections, including opportunistic infections (see also "Special warnings and precautions for use"). Thus, the overall incidence of infections can increase (in particular of rhinitis, bronchitis and pneumonia).

Neoplams benign, malignant and unspecified (incl cysts and polyps).
The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some immunosuppressive agents.
General disorders and administration site conditions
Common: anorexia, weight loss (usually insignificant), asthenia

Immune system disorders
Common: mild allergic reactions

Very rare: severe anaphylactic/anaphylactoid reactions, vasculitis, including cutaneous necrotizing vasculitis

Hepatobiliary disorders
Common: elevation of liver parameters (transaminases [especially ALT]. less often gamma-GT, alkaline phosphatase, bilirubin)
Rare: hepatitis, jaundice/cholestasis
Very rare: severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal

Reproductive system and breast disorders

Not known: marginal (reversible) decreases in sperm concentration, total sperm count and rapid progressive motility
Pyschiatric disorders
Uncommon: anxiety

4.9 Overdose

Symptoms

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 and children. There were no adverse events reported in the majority of case reports of overdose. Adverse events consistent with the safety profile for leflunomide were: the most frequently observed adverse events were abdominal pain, nausea, diarrhoea, elevated liver enzymes, anaemia, leucopenia, pruritus and rash.

Management

In the event of an overdose or toxicity, colestyramine or active charcoal is recommended to accelerate elimination. Colestyramine 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% ratio in 48 hours.

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 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 dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressive agents
ATC code: L04AA13.

Human pharmacology

Leflunomide is a disease-modifying anti-rheumatic agent with antiproliferative properties.

Animal pharmacology

Leflunomide is effective in animal models of arthritis and of other autoimmune diseases and transplantation, mainly if administered during the sensitisation phase. It has immunomodulating/ immunosuppressive characteristics, acts as an antiproliferative agent, and displays anti-inflammatory properties. Leflunomide exhibits the best protective effects on animal models of autoimmune diseases when administered in the early phase of the disease progression.

In vivo, it is rapidly and almost completely metabolised to A771726 which is active *in vitro*, and is

presumed to be responsible for the therapeutic effect.

Mechanism of action

A771726, the active metabolite of leflunomide, inhibits the human enzyme dihydroorotate dehydrogenase (DHODH) and exhibits antiproliferative activity.

5.2 Pharmacokinetic properties

General Characteristics

Leflunomide is rapidly converted to the active metabolite, A771726, by first-pass metabolism (ring opening) in gut wall and liver. In a study with radiolabelled ^{14}C-leflunomide in three healthy volunteers, no unchanged leflunomide was detected in plasma, urine or faeces. In other studies, unchanged leflunomide levels in plasma have rarely been detected, however, at ng/ml plasma levels. The only plasma-radiolabelled metabolite detected was A771726. This metabolite is responsible for essentially all the *in vivo* activity of BAGEDA.

Absorption

Excretion data from the ^{14}C study indicated that at least about 82 to 95% of the dose is absorbed. The time to peak plasma concentrations of A771726 is very variable; peak plasma levels can occur between 1 hour and 24 hours after single administration. Leflunomide can be administered with food, since the extent of absorption is comparable in the fed and fasting state. Due to the very long half-life of A771726 (approximately 2 weeks), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state levels of A771726. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. At a dose level of 20 mg/day, average plasma concentration of A771726 at steady state is approximately 35 µg/ml. At steady state plasma levels accumulate about 33- to 35-fold compared with single dose.

Distribution

In human plasma, A771726 is extensively bound to protein (albumin). The unbound fraction of A771726 is about 0.62%. Binding of A771726 is linear in the therapeutic concentration range. Binding of A771726 appeared slightly reduced and more variable in plasma from patients with rheumatoid arthritis or chronic renal insufficiency. The extensive protein binding of A771726 could lead to displacement of other highly-bound drugs. *In vitro* plasma protein binding interaction studies with warfarin at clinically relevant concentrations, however, showed no interaction. Similar studies showed that ibuprofen and diclofenac did not displace A771726, whereas the unbound fraction of A771726 is increased 2- to 3-fold in the presence of tolbutamide. A771726 displaced ibuprofen, diclofenac and tolbutamide but the unbound fraction of these drugs is only increased by 10% to 50%. There is no indication that these effects are of clinical relevance. Consistent with extensive protein binding A771726 has a low apparent volume of distribution (approximately 11 litres). There is no preferential uptake in erythrocytes.

Biotransformation

Leflunomide is metabolised to one primary (A771726) and many minor metabolites including TFMA (4-trifluoromethylaniline). The metabolic biotransformation of leflunomide to A771726 and subsequent metabolism of A771726 is not controlled by a single enzyme and has been shown to ocur in microsomal and cytosolic cellular fractions. Interaction studies with cimetidine (non-specific cytochrome P450 inhibitor) and rifampicin (non-specific cytochrome P450 inducer), indicate that *in vivo* CYP enzymes are involved in the metabolism of leflunomide only to a small extent.

Elimination

Elimination of A771726 is slow and characterised by an apparent clearance of about 31 ml/hr. The elimination half-life in patients is approximately 2 weeks. After administration of a radiolabelled dose of leflunomide, radioactivity was equally excreted in faeces, probably by biliary elimination, and in urine. A771726 was still detectable in urine and faeces 36 days after a single

administration. The principal urinary metabolites were glucuronide products derived from leflunomide (mainly in 0 to 24 hour samples) and an oxanilic acid derivative of A771726. The principal faecal component was A771726.

It has been shown in man that administration of an oral suspension of activated powdered charcoal or colestyramine leads to a rapid and significant increase in A771726 elimination rate and decline in plasma concentrations (see section 4.9). This is thought to be achieved by a gastrointestinal dialysis mechanism and/or by interrupting enterohepatic recycling.

Linear/Nonlinear Case

In multiple dose studies in patients with rheumatoid arthritis, the pharmacokinetic parameters of A771726 were linear over the dose range of 5 to 25 mg. In these studies, the clinical effect was closely related to the plasma concentration of A771726 and to the daily dose of leflunomide.

Characteristic properties in patients

Renal impairment

Leflunomide was administered as a single oral 100 mg dose to 3 haemodialysis patients and 3 patients on continuous peritoneal dialysis (CAPD). The pharmacokinetics of A771726 in CAPD subjects appeared to be similar to healthy volunteers. A more rapid elimination of A771726 was observed in haemodialysis subjects which was not due to extraction of drug in the dialysate.

Hepatic impairment

No data are available regarding treatment of patients with hepatic impairment. The active metabolite A771726 is extensively protein bound and cleared via hepatic metabolism and biliary secretion. These processes may be affected by hepatic dysfunction.

Paediatric population

The pharmacokinetics of A771726 following oral administration of leflunomide have been investigated in 73 pediatric patients with polyarticular course Juvenile Rheumatoid Arthritis (JRA) who ranged in age from 3 to 17 years. The results of a population pharmacokinetic analysis of these trials have demonstrated that pediatric patients with body weights ≤40 kg have a reduced systemic exposure (measured by Css) of A771726 relative to adult rheumatoid arthritis patients (see Section 4.2).

Geriatric Population

Pharmacokinetic data in elderly (>65 years) are limited but consistent with pharmacokinetics in younger adults.

5.3 Preclinical safety data

Leflunomide, administered orally and intraperitoneally, has been studied in acute toxicity studies in mice and rats. Repeated oral administration of leflunomide to mice for up to 3 months, to rats and dogs for up to 6 months and to monkeys for up to 1 month's duration revealed that the major target organs for toxicity were bone marrow, blood, gastrointestinal tract, skin, spleen, thymus and lymph nodes. The main effects were anaemia, leucopenia, decreased platelet counts and panmyelopathy and reflect the basic mode of action of the compound (inhibition of DNA synthesis). In rats and dogs, Heinz bodies and/or Howell-Jolly bodies were found. Other effects found on heart, liver, cornea and respiratory tract could be explained as infections due to immunosuppression. Toxicity in animals was found at doses equivalent to human therapeutic doses.

Leflunomide was not mutagenic. However, the minor metabolite TFMA (4-trifluoromethylaniline) caused clastogenicity and point mutations in vitro, whilst insufficient information was available on its potential to exert this effect *in vivo*.

In a carcinogenicity study in rats, leflunomide did not show carcinogenic potential. In a carcinogenicity study in mice an increased incidence of malignant lymphoma occurred in males of the highest dose group, considered to be due to the immunosuppressive activity of leflunomide. In female mice an increased incidence, dose-dependent, of bronchiolo-alveolar adenomas and carcinomas of the lung was noted. The relevance of the findings in mice relative to the clinical use of leflunomide is uncertain.

Leflunomide was not antigenic in animal models.
Leflunomide was embryotoxic and teratogenic in rats and rabbits at doses in the human therapeutic range and exerted adverse effects on male reproductive organs in repeated dose toxicity studies.

Fertility was not reduced.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Lactose anhydrous
Pregelatinized corn starch
Hydroxypropyl cellulose (HPC) LH-11
Polyvinyl pyrrolidone K30
Sodium starch glycolate
Colloidal silicon dioxide
Magnesium stearate
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol / polyethylene glycol
Talc

Yellow iron oxide (E172)

Tartrazine (E102)

Sunset yellow FCF (E110)

Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30ºC at room temperature.

6.5 Nature and contents of container

It is presented as 30 tablets in Oriented Polyamide/Aluminium/PVC film with Aluminium blister foil in cardboard box.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRANT

Goldplus Universal Pte Ltd

103 Kallang Avenue #06-02, Singapore 339504

8. MARKETING AUTHORISATION NUMBER