Public Assessment Report

Decentralised Procedure

LEFLUNOMIDE 10 MG FLM-COATED TABLETS
LEFLUNOMIDE 20 MG FLM-COATED TABLETS

Procedure No: UK/H/2957/001-2/DC

UK Licence No: PL 35533/0008-9

ASPIRE PHARMA LIMITED
LAY SUMMARY

On 10 May 2011, Ireland and the UK agreed to grant Marketing Authorisations to Aspire Pharma Limited for the medicinal products Leflunomide 10 mg and 20 mg film-coated tablets (PL 35533/0008-9; UK/H/2957/001-2/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 17 June 2011.

Leflunomide 10 mg and 20 mg film-coated tablets are Prescription-Only Medicines (POM) used in the treatment of adult patients with active rheumatoid arthritis or with active psoriatic arthritis.

Leflunomide belongs to a group of medicines called anti-rheumatic medicines.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Leflunomide 10 mg and 20 mg film-coated tablets outweigh the risks and Marketing Authorisations were granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module 1: Information about initial procedure</th>
<th>Page 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>Page 5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflets</td>
<td>Page 27</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>Page 29</td>
</tr>
<tr>
<td>Module 5: Scientific discussion during initial procedure</td>
<td>Page 31</td>
</tr>
<tr>
<td>I Introduction</td>
<td></td>
</tr>
<tr>
<td>II About the product</td>
<td></td>
</tr>
<tr>
<td>III Scientific Overview and discussion</td>
<td></td>
</tr>
<tr>
<td>III.1 Quality aspects</td>
<td></td>
</tr>
<tr>
<td>III.2 Non-clinical aspects</td>
<td></td>
</tr>
<tr>
<td>III.3 Clinical aspects</td>
<td></td>
</tr>
<tr>
<td>IV Overall Conclusions and benefit-risk assessment</td>
<td></td>
</tr>
<tr>
<td>Module 6 Steps taken after initial procedure</td>
<td>Page 39</td>
</tr>
</tbody>
</table>
**Module 1**

| **Product Name**       | Leflunomide 10 mg film-coated tablets  
Leflunomide 20 mg film-coated tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Leflunomide</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated tablet</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>10 mg and 20 mg</td>
</tr>
</tbody>
</table>
| **MA Holder**          | Aspire Pharma Ltd, Antrobus House Business Centre  
18 College Street, Petersfield, Hampshire, GU31 4AD, UK. |
| **Reference Member State (RMS)** | UK                                                                             |
| **Concerned Member State (CMS)** | Ireland                                                                         |
| **Procedure Number**   | UK/H/2957/001-2/DC                                                                 |
| **Timetable**          | Day 208– 10 May 2011                                                               |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Leflunomide tablets 10mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Leflunomide tablets 10mg film-coated tablets:
Each tablet contains 10mg of leflunomide.
Excipient: each tablet contains 19.80 mg of lactose monohydrate equivalent to 18.81 mg of lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
- Leflunomide 10mg film-coated tablets are white, round biconvex tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Leflunomide is indicated for the treatment of adult patients with:
• active rheumatoid arthritis as a “disease-modifying antirheumatic drug” (DMARD),
• active psoriatic arthritis.

Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.

Moreover, switching from leflunomide to another DMARD without following the washout procedure (see section 4.4) may also increase the risk of serious adverse reactions even for a long time after the switching.

4.2 Posology and method of administration
The treatment should be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.

Alanine aminotransferase (ALT) or serum glutamopyruvate transferase (SGPT) and a complete blood cell count, including a differential white blood cell count and a platelet count, must be checked simultaneously and with the same frequency:
• before initiation of leflunomide,
• every two weeks during the first six months of treatment, and
• every 8 weeks thereafter (see section 4.4).

Posology
Leflunomide therapy is started with a loading dose of 100 mg once daily for 3 days.
• The recommended maintenance dose for rheumatoid arthritis is leflunomide 10 mg to 20 mg once daily. Patients may be started on leflunomide 10 mg or 20 mg depending on the severity (activity) of the disease.
• The recommended maintenance dose for patients with psoriatic arthritis is 20 mg once daily (see section 5.1).

The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months. There is no dose adjustment recommended in patients with mild renal insufficiency. No dosage adjustment is required in patients above 65 years of age.

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

Administration
Leflunomide tablets tablets should be swallowed whole with sufficient amounts of liquid. The extent of leflunomide absorption is not affected if it is taken with food.
4.3 Contraindications
• Hypersensitivity to the active substance (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients.
• Patients with impairment of liver function.
• Patients with severe immunodeficiency states, e.g. 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.
• 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 start of treatment with leflunomide.
• Breast-feeding women (see section 4.6).

4.4 Special warnings and precautions for use
Concomitant administration of hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) is not advisable.

The active metabolite of leflunomide, A771726, has a long half-life, usually 1 to 4 weeks. Serious undesirable effects might occur (e.g. hepatotoxicity, haematotoxicity or allergic reactions, see below), even if the treatment with leflunomide has been stopped. Therefore, when such toxicities occur or if for any other reason A771726 needs to be cleared rapidly from the body, the washout procedure has to be followed. The procedure may be repeated as clinically necessary.

For washout procedures and other recommended actions in case of desired or unintended pregnancy, see section 4.6.

Liver reactions
Rare cases of severe liver injury, including cases with fatal outcome, have been reported during treatment with leflunomide. Most of the cases occurred within the first 6 months of treatment. Cotreatment with other hepatotoxic medicinal products was frequently present. It is considered essential that monitoring recommendations are strictly adhered to.

ALT (SGPT) must be checked before initiation of leflunomide and at the same frequency as the complete blood cell count (every two weeks) during the first six months of treatment and every 8 weeks thereafter.

For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, dose reduction from 20 mg to 10 mg may be considered and monitoring must be performed weekly. If ALT (SGPT) elevations of more than 2-fold the upper limit of normal persist or if ALT elevations of more than 3-fold the upper limit of normal are present, leflunomide must be discontinued and wash-out procedures initiated. It is recommended that monitoring of liver enzymes be maintained after discontinuation of leflunomide treatment, until liver enzyme levels have normalised.

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

Since the active metabolite of leflunomide, A771726, is highly protein bound and cleared via hepatic metabolism and biliary secretion, plasma levels of A771726 are expected to be increased in patients with hypoproteinaemia. Leflunomide tablets is contraindicated in patients with severe hypoproteinaemia or impairment of liver function (see section 4.3).

Haematological reactions
Together with ALT, a complete blood cell count, including differential white blood cell count and platelets, must be performed before start of leflunomide treatment as well as every 2 weeks for the first 6 months of treatment and every 8 weeks thereafter.

In patients with pre-existing anaemia, 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 haematological
disorders is increased. If such effects occur, a washout (see below) to reduce plasma levels of A771726 should be considered.

In case of severe haematological reactions, including pancytopenia, Leflunomide tablets and any concomitant myelosuppressive treatment must be discontinued and a leflunomide washout procedure initiated.

**Combinations with other treatments**
The use of leflunomide with antimalarials used in rheumatic diseases (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive agents (with the exception of methotrexate, see section 4.5) has not been studied up to now. The risk associated with combination therapy, in particular in long-term treatment, is unknown. Since such therapy can lead to additive or even synergistic toxicity (e.g. hepato- or haematotoxicity), combination with another DMARD (e.g. methotrexate) is not advisable.

Caution is advised when leflunomide is given together with drugs, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin, phenprocoumon and tolbutamide.

**Switching to other treatments**
As leflunomide has a long persistence in the body, a switching to another DMARD (e.g. methotrexate) without performing the washout procedure (see below) may raise the possibility of additive risks even for a long time after the switching (i.e. kinetic interaction, organ toxicity).

Similarly, recent treatment with hepatotoxic or haematotoxic medicinal products (e.g. methotrexate) may result in increased side effects; therefore, the initiation of leflunomide treatment has to carefully be considered regarding these benefit/risk aspects and closer monitoring is recommended in the initial phase after switching.

**Skin reactions**
In case of ulcerative stomatitis, leflunomide administration should be discontinued.

Very rare cases of Stevens Johnson syndrome or toxic epidermal necrolysis 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, Leflunomide tablets and any other possibly associated treatment must be discontinued, and a leflunomide washout procedure initiated immediately. A complete washout is essential in such cases. In such cases re-exposure to leflunomide is contra-indicated (see section 4.3).

**Infections**
It is known that medicinal products with immunosuppressive properties - like leflunomide - may cause patients to be more susceptible to infections, including opportunistic infections. Infections may be more severe in nature and may, therefore, require early and vigorous treatment. In the event that severe, uncontrolled infections occur, it may be necessary to interrupt leflunomide treatment and administer a washout procedure as described below.

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

Patients with tuberculin reactivity must be carefully monitored because of the risk of tuberculosis reactivation.

**Respiratory reactions**
Interstitial lung disease has been reported during treatment with leflunomide (see section 4.8). 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.

**Blood pressure**
Blood pressure must be checked before the start of leflunomide treatment and periodically thereafter.

**Procreation (recommendations for men)**

Male patients should be aware of the possible male-mediated foetal toxicity. Reliable contraception during treatment with leflunomide should also be guaranteed.
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 leflunomide and taking colestyramine 8 g 3 times daily for 11 days or 50 g of activated powdered charcoal 4 times daily for 11 days.

In either case the A771726 plasma concentration is then measured for the first time. Thereafter, the A771726 plasma concentration must be determined again after an interval of at least 14 days. If both plasma concentrations are below 0.02 mg/l, and after a waiting period of at least 3 months, the risk of foetal toxicity is very low.

**Washout procedure**

Colestyramine 8 g is administered 3 times daily. Alternatively, 50 g of activated powdered charcoal is administered 4 times daily. Duration of a complete washout is usually 11 days. The duration may be modified depending on clinical or laboratory variables.

**Lactose**

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

### 4.5 Interaction with other medicinal products and other forms of interaction

Interactions studies have only been performed in adults. Increased side effects may occur in case of recent or concomitant use of hepatotoxic or haematotoxic drugs or when leflunomide treatment is followed by such drugs without a washout period (see also guidance concerning combination with other treatments, section 4.4). Therefore, closer monitoring of liver enzymes and haematological parameters is recommended in the initial phase after switching.

In a small (n=30) study with co-administration of leflunomide (10 to 20 mg per day) with methotrexate (10 to 25 mg per week) a 2- to 3-fold elevation in liver enzymes was seen on 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.

In patients with rheumatoid arthritis, no pharmacokinetic interaction between the leflunomide (10 to 20 mg per day) and methotrexate (10 to 25 mg per week) was demonstrated.

It is recommended that patients receiving leflunomide are not treated with colestyramine or activated powdered charcoal because this leads to a rapid and significant decrease in plasma A771726 (the active metabolite of leflunomide; see also section 5) concentration. The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of A771726.

If the patient is already receiving nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids, these may be continued after starting leflunomide.

The enzymes involved in the metabolism of leflunomide and its metabolites are not exactly known. An *in vivo* interaction study with cimetidine (non-specific cytochrome P450 inhibitor) has demonstrated a lack of a significant interaction. Following concomitant administration of a single dose of leflunomide to subjects receiving multiple doses of rifampicin (non-specific cytochrome P450 inducer) A771726 peak levels were increased by approximately 40%, whereas the AUC was not significantly changed. The mechanism of this effect is unclear.

*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. Caution is advised when leflunomide is given together with drugs, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin, phenprocoumon and tolbutamide. In a study in which leflunomide was given concomitantly with a triphasic oral contraceptive pill containing 30 μg ethinyloestradiol to healthy female volunteers, there was no reduction in contraceptive activity of the pill, and A771726 pharmacokinetics were within predicted ranges.

**Vaccinations**

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

**Pregnancy**
The active metabolite of leflunomide, A771726 is suspected to cause serious birth defects when administered during pregnancy. Leflunomide tablets is contraindicated in pregnancy (see section 4.3).

Women of childbearing potential have to use effective contraception during and up to 2 years after treatment (see “waiting period” below) or up to 11 days after treatment (see abbreviated “washout period” below).

The 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, and if positive, the physician and patient must discuss the risk to the 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 foetus from leflunomide.

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]).

For women receiving leflunomide treatment and who wish to become pregnant, one of the following procedures is recommended in order to ascertain that the foetus is not exposed to toxic concentrations of A771726 (target concentration below 0.02 mg/l):

**Waiting period**
A771726 plasma levels can be expected to be above 0.02 mg/l for a prolonged period. The concentration may be expected to decrease below 0.02 mg/l about 2 years after stopping the treatment with leflunomide.

After a 2-year waiting period, the A771726 plasma concentration is measured for the first time. Thereafter, the A771726 plasma concentration must be determined again after an interval of at least 14 days. If both plasma concentrations are below 0.02 mg/l no teratogenic risk is to be expected.

For further information on the sample testing please contact the Marketing Authorisation Holder or its local representative (see section 7).

**Washout procedure**
After stopping treatment with leflunomide:
- colestyramine 8 g is administered 3 times daily for a period of 11 days,
- alternatively, 50 g of activated powdered charcoal is administered 4 times daily for a period of 11 days.

However, also following either of the washout procedures, verification by 2 separate tests at an interval of at least 14 days and a waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0.02 mg/l and fertilisation is required.

Women of childbearing potential should be told that a waiting period of 2 years after treatment discontinuation is required before they may become pregnant. 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.

Both colestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens such that reliable contraception with oral contraceptives may not be guaranteed during the washout procedure with colestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended.

**Lactation**
Animal studies indicate that leflunomide or its metabolites pass into breast milk. Breast-feeding women must, therefore, not receive leflunomide.
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

The most frequently adverse effects reported commonly (≥1/100 to <1/10) with leflunomide are: mild increase in blood pressure, leucopenia, paraesthesia, headache, dizziness, diarrhoea, nausea, vomiting, oral mucosal disorders (e.g. aphthous stomatitis, mouth ulceration), abdominal pain, increased hair loss, eczema, rash (including maculo-papular rash), pruritus, dry skin, tenosynovitis, CPK increased, anorexia, weight loss (usually insignificant), asthenia, mild allergic reactions and elevation of liver parameters (transaminases especially ALT), less often gamma-GT, alkaline phosphatise, bilirubin)

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.

Infections and infestations
Rare: severe infections, including sepsis which may be fatal

Like other agents with immunosuppressive potential, leflunomide may increase susceptibility to infections, including opportunistic infections (see also section 4.4). Thus, the overall incidence of infections can increase (in particular of rhinitis, bronchitis and pneumonia).

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some immunosuppressive agents.

Blood and lymphatic system disorders
Common: leucopenia (leucocytes ≥2 G/l)
Uncommon: anaemia, mild thrombocytopenia (platelets <100 G/l)
Rare: pancytopenia (probably by antiproliferative mechanism), leucopenia (leucocytes <2 G/l), eosinophilia
Very rare: agranulocytosis
Recent, concomitant or consecutive use of potentially myelotoxic agents may be associated with a higher risk of haematological effects.

Immune system disorders
Common: mild allergic reactions
Very rare: severe anaphylactic/anaphylactoid reactions, vasculitis, including cutaneous necrotizing vasculitis

Metabolism and nutrition disorders
Common: CPK increased
Uncommon: hypokalaemia, hyperlipidemia, hypophosphataemia
Rare: LDH increased
Not known: hypouricemia

Psychiatric disorders
Uncommon: anxiety

Nervous system disorders
Common: paraesthesia, headache, dizziness
Very rare: peripheral neuropathy

Cardiac disorders
Common: mild increase in blood pressure
Rare: severe increase in blood pressure

Respiratory, thoracic and mediastinal disorders
Rare: interstitial lung disease (including interstitial pneumonitis), which may be fatal
**Gastrointestinal disorders**
Common: diarrhoea, nausea, vomiting, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain
Uncommon: taste disturbances
Very rare: pancreatitis

**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

**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

**Musculoskeletal and connective tissue disorders**
Common: tenosynovitis
Uncommon: tendon rupture

**Renal and urinary disorders**
Not known: renal failure

**Reproductive system and breast disorders**
Not known: marginal (reversible) decreases in sperm concentration, total sperm count and rapid progressive motility

**General disorders and administration site conditions**
Common: anorexia, weight loss (usually insignificant), asthenia

### 4.9 Overdose

**Symptoms**
There have been reports of chronic overdose in patients taking Leflunomide tablets 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: abdominal pain, nausea, diarrhoea, elevated liver enzymes, anaemia, leucopenia, pruritus and rash.

**Management**
In the event of an overdose or toxicity, colestyramine or 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% 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 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 dialysable.

### 5 PHARMACOLOGICAL PROPERTIES

5.1 **Pharmacodynamic properties**

**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.

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

**Rheumatoid arthritis**
The efficacy of Leflunomide tablets in the treatment of rheumatoid arthritis was demonstrated in 4 controlled trials (1 in phase II and 3 in phase III). The phase II trial, study YU203, randomised 402 subjects with active rheumatoid arthritis to placebo (n=102), leflunomide 5 mg (n=95), 10 mg (n=101) or 25 mg/day (n=104). The treatment duration was 6 months.

All leflunomide patients in the phase III trials used an initial dose of 100 mg for 3 days.

Study MN301 randomised 358 subjects with active rheumatoid arthritis to leflunomide 20 mg/day (n=133), sulphasalazine 2 g/day (n=133), or placebo (n=92). Treatment duration was 6 months.

Study MN303 was an optional 6-month blinded continuation of MN301 without the placebo arm, resulting in a 12-month comparison of leflunomide and sulphasalazine.

Study MN302 randomised 999 subjects with active rheumatoid arthritis to leflunomide 20 mg/day (n=501) or methotrexate at 7.5 mg/week increasing to 15 mg/week (n=498). Folate supplementation was optional and only used in 10% of patients. Treatment duration was 12-months. Study US301 randomised 482 subjects with active rheumatoid arthritis to leflunomide 20 mg/day (n=182), methotrexate 7.5 mg/week increasing to 15 mg/week (n=182), or placebo (n=118). All patients received folate 1 mg bid. Treatment duration was 12 months.

Leflunomide at a daily dose of at least 10 mg (10 to 25 mg in study YU203, 20 mg in studies MN301 and US301) was statistically significantly superior to placebo in reducing the signs and symptoms of rheumatoid arthritis in all 3 placebo-controlled trials. The ACR (American College of Rheumatology) response rates in study YU203 were 27.7% for placebo, 31.9% for 5 mg, 50.5% for 10 mg and 54.5% for 25 mg/day. In the phase III trials, the ACR response rates for leflunomide 20 mg/day vs. placebo were 54.6% vs. 28.6% (study MN301), and 49.4% vs. 26.3% (study US301). After 12 months with active treatment, the ACR response rates in leflunomide patients were 52.3% (studies MN301/303), 50.5% (study MN302) and 49.4% (study US301), compared to 53.8% (studies MN301/303) in sulphasalazine patients, 64.8% (study MN302), and 43.9% (study US301) in methotrexate patients. In study MN302 leflunomide was significantly less effective than methotrexate. However, in study US301 no significant differences were observed between leflunomide and methotrexate in the primary efficacy parameters. No difference was observed between leflunomide and sulphasalazine (study MN301). The leflunomide treatment effect was evident by 1 month, stabilised by 3 to 6 months and continued throughout the course of treatment.

A randomised, double-blind, parallel-group non-inferiority study compared the relative efficacy of two different daily maintenance doses of leflunomide, 10 mg and 20 mg. From the results it can be concluded that efficacy results of the 20 mg maintenance dose were more favourable, on the other hand, the safety results favoured the 10 mg daily maintenance dose.

**Paediatrics**
Leflunomide was studied in a single multicenter, randomized, double-blind, active-controlled trial in 94 patients (47 per arm) with polyarticular course juvenile rheumatoid arthritis. Patients were 3–17 years of age with active polyarticular course JRA regardless of onset type and naive to methotrexate or leflunomide. In this trial, the loading dose and maintenance dose of leflunomide was based on three weight categories: <20 kg, 20-40 kg, and >40 kg. After 16 weeks treatment, the difference in response rates was statistically significant in favour of methotrexate for the JRA Definition of Improvement (DOI) ≥30% (p=0.02). In responders, this response was maintained during 48 weeks (see section 4.2).
The pattern of adverse events of leflunomide and methotrexate seems to be similar, but the dose used in lighter subjects resulted in a relatively low exposure (see section 5.2). These data do not allow an effective and safe dose recommendation.

Psoriatic arthritis
The efficacy of Leflunomide tablets was demonstrated in one controlled, randomised, double blind study 3L01 in 188 patients with psoriatic arthritis, treated at 20 mg/day. Treatment duration was 6 months.

Leflunomide 20 mg/day was significantly superior to placebo in reducing the symptoms of arthritis in patients with psoriatic arthritis: the PsARC (Psoriatic Arthritis treatment Response Criteria) responders were 59% in the leflunomide group and 29.7% in the placebo group by 6 months (p<0.0001). The effect of leflunomide on improvement of function and on reduction of skin lesions was modest.

5.2 Pharmacokinetic properties
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 14C-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 Leflunomide tablets.

Absorption
Excretion data from the 14C 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. 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. 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.

Metabolism
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 occur in microsomal and cytosolic cellular fractions. Interaction studies with cimetidine (non-specific CYP enzyme 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.

**Pharmacokinetics in renal failure**

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.

**Pharmacokinetics in liver failure**

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.

**Pharmacokinetics in paediatrics**

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).

**Pharmacokinetics in elderly**

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 pannmyelopathy 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

**Tablet core:**

- Cellulose microcrystalline
- Pregelatinized starch (maize starch 1500)
- Povidone (E1201) (K30)
Crospovidone (E1202) (Type A)
Silica colloidal anhydrous
Magnesium stearate (E470b)
Lactose monohydrate

Film-coating:
Opadry II White OY-LS-28908 in the 10mg
[Consisting of: Titanium dioxide (E171), Lactose monohydrate, Hypromellose 15cP (E464),
Macrogol/PEG 4000, Hypromellose 3cP (E464), Hypromellose 50cP (E464)]

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.
Once opened: 30 days

6.4 Special precautions for storage
Bottle: Keep the container tightly closed.

6.5 Nature and contents of container
Bottle: 30 ml white HDPE container, with tamper-evident closure with an integrated desiccant or
dessicant sachet, containing 30 film-coated tablets, respectively.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Aspire Pharma Ltd
Antrobus House Business Centre
18 College Street
Petersfield
Hampshire
GU31 4AD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 35533/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/06/2011

10 DATE OF REVISION OF THE TEXT
17/06/2011
1 NAME OF THE MEDICINAL PRODUCT
Leflunomide tablets 20mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 20mg of leflunomide.
Excipient: each tablet contains 38.40mg of lactose monohydrate equivalent to 36.48 mg of lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
- Leflunomide 20mg film-coated tablets are yellow, round biconvex, with a scoreline on one side. The score-line is for the purpose of identification only.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Leflunomide is indicated for the treatment of adult patients with:
• active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD),
• active psoriatic arthritis.

Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.

Moreover, switching from leflunomide to another DMARD without following the washout procedure (see section 4.4) may also increase the risk of serious adverse reactions even for a long time after the switching.

4.2 Posology and method of administration
The treatment should be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.

Alanine aminotransferase (ALT) or serum glutamopyruvate transferase (SGPT) and a complete blood cell count, including a differential white blood cell count and a platelet count, must be checked simultaneously and with the same frequency:
• before initiation of leflunomide,
• every two weeks during the first six months of treatment, and
• every 8 weeks thereafter (see section 4.4).

Posology
Leflunomide therapy is started with a loading dose of 100 mg once daily for 3 days.

• The recommended maintenance dose for rheumatoid arthritis is leflunomide 10 mg to 20 mg once daily. Patients may be started on leflunomide 10 mg or 20 mg depending on the severity (activity) of the disease.

• The recommended maintenance dose for patients with psoriatic arthritis is 20 mg once daily (see section 5.1).

The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months. There is no dose adjustment recommended in patients with mild renal insufficiency.

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

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

Administration
Leflunomide tablets tablets should be swallowed whole with sufficient amounts of liquid. The extent of leflunomide absorption is not affected if it is taken with food.

4.3 Contraindications
• Hypersensitivity to the active substance (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients.
• Patients with impairment of liver function.
• Patients with severe immunodeficiency states, e.g. 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.
• Pregnancy, 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 start of treatment with leflunomide.
• Breast-feeding women (see section 4.6).

4.4 Special warnings and precautions for use
Concomitant administration of hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) is not advisable.

The active metabolite of leflunomide, A771726, has a long half-life, usually 1 to 4 weeks. Serious undesirable effects might occur (e.g. hepatotoxicity, haematotoxicity or allergic reactions, see below), even if the treatment with leflunomide has been stopped. Therefore, when such toxicities occur or if for any other reason A771726 needs to be cleared rapidly from the body, the washout procedure has to be followed. The procedure may be repeated as clinically necessary.

For washout procedures and other recommended actions in case of desired or unintended pregnancy, see section 4.6.

Liver reactions
Rare cases of severe liver injury, including cases with fatal outcome, have been reported during treatment with leflunomide. Most of the cases occurred within the first 6 months of treatment. Cotreatment with other hepatotoxic medicinal products was frequently present. It is considered essential that monitoring recommendations are strictly adhered to.

ALT (SGPT) must be checked before initiation of leflunomide and at the same frequency as the complete blood cell count (every two weeks) during the first six months of treatment and every 8 weeks thereafter.

For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, dose reduction from 20 mg to 10 mg may be considered and monitoring must be performed weekly. If ALT (SGPT) elevations of more than 2-fold the upper limit of normal persist or if ALT elevations of more than 3-fold the upper limit of normal are present, leflunomide must be discontinued and wash-out procedures initiated. It is recommended that monitoring of liver enzymes be maintained after discontinuation of leflunomide treatment, until liver enzyme levels have normalised.

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

Since the active metabolite of leflunomide, A771726, is highly protein bound and cleared via hepatic metabolism and biliary secretion, plasma levels of A771726 are expected to be increased in patients with hypoproteinaemia. Leflunomide tablets is contraindicated in patients with severe hypoproteinaemia or impairment of liver function (see section 4.3).

Haematological reactions
Together with ALT, a complete blood cell count, including differential white blood cell count and platelets, must be performed before start of leflunomide treatment as well as every 2 weeks for the first 6 months of treatment and every 8 weeks thereafter.

In patients with pre-existing anaemia, 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 haematological disorders is increased. If such effects occur, a washout (see below) to reduce plasma levels of A771726 should be considered.
In case of severe haematological reactions, including pancytopenia, Leflunomide tablets and any concomitant myelosuppressive treatment must be discontinued and a leflunomide washout procedure initiated.

**Combinations with other treatments**
The use of leflunomide with antimalarials used in rheumatic diseases (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive agents (with the exception of methotrexate, see section 4.5) has not been studied up to now. The risk associated with combination therapy, in particular in long-term treatment, is unknown. Since such therapy can lead to additive or even synergistic toxicity (e.g. hepato- or haematotoxicity), combination with another DMARD (e.g. methotrexate) is not advisable.

Caution is advised when leflunomide is given together with drugs, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin, phenprocoumon and tolbutamide.

**Switching to other treatments**
As leflunomide has a long persistence in the body, a switching to another DMARD (e.g. methotrexate) without performing the washout procedure (see below) may raise the possibility of additive risks even for a long time after the switching (i.e. kinetic interaction, organ toxicity).

Similarly, recent treatment with hepatotoxic or haematotoxic medicinal products (e.g. methotrexate) may result in increased side effects; therefore, the initiation of leflunomide treatment has to carefully be considered regarding these benefit/risk aspects and closer monitoring is recommended in the initial phase after switching.

**Skin reactions**
In case of ulcerative stomatitis, leflunomide administration should be discontinued.

Very rare cases of Stevens Johnson syndrome or toxic epidermal necrolysis 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, Leflunomide tablets and any other possibly associated treatment must be discontinued, and a leflunomide washout procedure initiated immediately. A complete washout is essential in such cases. In such cases re-exposure to leflunomide is contra-indicated (see section 4.3).

**Infections**
It is known that medicinal products with immunosuppressive properties - like leflunomide - may cause patients to be more susceptible to infections, including opportunistic infections. Infections may be more severe in nature and may, therefore, require early and vigorous treatment. In the event that severe, uncontrolled infections occur, it may be necessary to interrupt leflunomide treatment and administer a washout procedure as described below.

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

Patients with tuberculin reactivity must be carefully monitored because of the risk of tuberculosis reactivation.

**Respiratory reactions**
Interstitial lung disease has been reported during treatment with leflunomide (see section 4.8). 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.

**Blood pressure**
Blood pressure must be checked before the start of leflunomide treatment and periodically thereafter.

**Procreation (recommendations for men)**
Male patients should be aware of the possible male-mediated foetal toxicity. Reliable contraception during treatment with leflunomide should also be guaranteed.

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 leflunomide and taking colestyramine 8 g 3 times daily for 11 days or 50 g of activated powdered charcoal 4 times daily for 11 days.

In either case the A771726 plasma concentration is then measured for the first time. Thereafter, the A771726 plasma concentration must be determined again after an interval of at least 14 days. If both plasma concentrations are below 0.02 mg/l, and after a waiting period of at least 3 months, the risk of foetal toxicity is very low.

**Washout procedure**
Colestyramine 8 g is administered 3 times daily. Alternatively, 50 g of activated powdered charcoal is administered 4 times daily. Duration of a complete washout is usually 11 days. The duration may be modified depending on clinical or laboratory variables.

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

### 4.5 Interaction with other medicinal products and other forms of interaction

Interactions studies have only been performed in adults.

Increased side effects may occur in case of recent or concomitant use of hepatotoxic or haematotoxic drugs or when leflunomide treatment is followed by such drugs without a washout period (see also guidance concerning combination with other treatments, section 4.4). Therefore, closer monitoring of liver enzymes and haematological parameters is recommended in the initial phase after switching.

In a small (n=30) study with co-administration of leflunomide (10 to 20 mg per day) with methotrexate (10 to 25 mg per week) a 2- to 3-fold elevation in liver enzymes was seen on 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.

In patients with rheumatoid arthritis, no pharmacokinetic interaction between the leflunomide (10 to 20 mg per day) and methotrexate (10 to 25 mg per week) was demonstrated.

It is recommended that patients receiving leflunomide are not treated with colestyramine or activated powdered charcoal because this leads to a rapid and significant decrease in plasma A771726 (the active metabolite of leflunomide; see also section 5) concentration. The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of A771726.

If the patient is already receiving nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids, these may be continued after starting leflunomide.

The enzymes involved in the metabolism of leflunomide and its metabolites are not exactly known. An in vivo interaction study with cimetidine (non-specific cytochrome P450 inhibitor) has demonstrated a lack of a significant interaction. Following concomitant administration of a single dose of leflunomide to subjects receiving multiple doses of rifampicin (non-specific cytochrome P450 inducer) A771726 peak levels were increased by approximately 40%, whereas the AUC was not significantly changed.

The mechanism of this effect is unclear.

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. Caution is advised when leflunomide is given together with drugs, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin, phenprocoumon and tolbutamide.

In a study in which leflunomide was given concomitantly with a triphasic oral contraceptive pill containing 30 μg ethinylestradiol to healthy female volunteers, there was no reduction in contraceptive activity of the pill, and A771726 pharmacokinetics were within predicted ranges.

**Vaccinations**
No clinical data are available on the efficacy and safety of vaccinations under leflunomide treatment. Vaccination with live attenuated vaccines is, however, not recommended. The long half-life of leflunomide should be considered when contemplating administration of a live attenuated vaccine after stopping Leflunomide tablets.
4.6 Pregnancy and lactation

Pregnancy
The active metabolite of leflunomide, A771726 is suspected to cause serious birth defects when administered during pregnancy. Leflunomide tablets is contraindicated in pregnancy (see section 4.3).

Women of childbearing potential have to use effective contraception during and up to 2 years after treatment (see “waiting period” below) or up to 11 days after treatment (see abbreviated “washout period” below).

The 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, and if positive, the physician and patient must discuss the risk to the 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 foetus from leflunomide.

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]).

For women receiving leflunomide treatment and who wish to become pregnant, one of the following procedures is recommended in order to ascertain that the foetus is not exposed to toxic concentrations of A771726 (target concentration below 0.02 mg/l):

Waiting period
A771726 plasma levels can be expected to be above 0.02 mg/l for a prolonged period. The concentration may be expected to decrease below 0.02 mg/l about 2 years after stopping the treatment with leflunomide.

After a 2-year waiting period, the A771726 plasma concentration is measured for the first time. Thereafter, the A771726 plasma concentration must be determined again after an interval of at least 14 days. If both plasma concentrations are below 0.02 mg/l no teratogenic risk is to be expected.

For further information on the sample testing please contact the Marketing Authorisation Holder or its local representative (see section 7).

Washout procedure
After stopping treatment with leflunomide:
• colestyramine 8 g is administered 3 times daily for a period of 11 days,
• alternatively, 50 g of activated powdered charcoal is administered 4 times daily for a period of 11 days.

However, also following either of the washout procedures, verification by 2 separate tests at an interval of at least 14 days and a waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0.02 mg/l and fertilisation is required.

Women of childbearing potential should be told that a waiting period of 2 years after treatment discontinuation is required before they may become pregnant. 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.

Both colestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens such that reliable contraception with oral contraceptives may not be guaranteed during the washout procedure with colestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended.

Lactation
Animal studies indicate that leflunomide or its metabolites pass into breast milk. Breast-feeding women must, therefore, not receive leflunomide.

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
The most frequently adverse effects reported commonly (≥1/100 to <1/10) with leflunomide are: mild increase in blood pressure, leucopenia, paraesthesia, headache, dizziness, diarrhoea, nausea, vomiting, oral mucosal disorders (e.g. aphthous stomatitis, mouth ulceration), abdominal pain, increased hair loss, eczema, rash (including maculo-papular rash), pruritus, dry skin, tenosynovitis, CPK increased, anorexia, weight loss (usually insignificant), asthenia, mild allergic reactions and elevation of liver parameters (transaminases (especially ALT), less often gamma-GT, alkaline phosphatase, bilirubin))

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.

Infections and infestations
Rare: severe infections, including sepsis which may be fatal
Like other agents with immunosuppressive potential, leflunomide may increase susceptibility to infections, including opportunistic infections (see also section 4.4). Thus, the overall incidence of infections can increase (in particular of rhinitis, bronchitis and pneumonia).

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some immunosuppressive agents.

Blood and lymphatic system disorders
Common: leucopenia (leucocytes >2 G/l)
Uncommon: anaemia, mild thrombocytopenia (platelets <100 G/l)
Rare: pancytopenia (probably by antiproliferative mechanism), leucopenia (leucocytes <2 G/l), eosinophilia
Very rare: agranulocytosis
Recent, concomitant or consecutive use of potentially myelotoxic agents may be associated with a higher risk of haematological effects.

Immune system disorders
Common: mild allergic reactions
Very rare: severe anaphylactic/anaphylactoid reactions, vasculitis, including cutaneous necrotizing vasculitis

Metabolism and nutrition disorders
Common: CPK increased
Uncommon: hypokalaemia, hyperlipidemia, hypophosphataemia
Rare: LDH increased
Not known: hypouricemia

Psychiatric disorders
Uncommon: anxiety

Nervous system disorders
Common: paraesthesia, headache, dizziness
Very rare: peripheral neuropathy

Cardiac disorders
Common: mild increase in blood pressure
Rare: severe increase in blood pressure

Respiratory, thoracic and mediastinal disorders
Rare: interstitial lung disease (including interstitial pneumonitis), which may be fatal

Gastrointestinal disorders
Common: diarrhoea, nausea, vomiting, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain
Uncommon: taste disturbances
Very rare: pancreatitis
Hepatobiliary disorders
Common: elevation of liver parameters (transaminases [especially ALT], less often gamma-GT, alkaline phosphatase, bilirubin)
Rare: hepatitis, jaundice/cholestatic
Very rare: severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal

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

Musculoskeletal and connective tissue disorders
Common: tenosynovitis
Uncommon: tendon rupture

Renal and urinary disorders
Not known: renal failure

Reproductive system and breast disorders
Not known: marginal (reversible) decreases in sperm concentration, total sperm count and rapid progressive motility

General disorders and administration site conditions
Common: anorexia, weight loss (usually insignificant), asthenia

4.9 Overdose
Symptoms
There have been reports of chronic overdose in patients taking Leflunomide tablets 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: abdominal pain, nausea, diarrhoea, elevated liver enzymes, anaemia, leucopenia, pruritus and rash.

Management
In the event of an overdose or toxicity, colestyramine or 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% 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 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 dialysable.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

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.
Mode of action

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

Rheumatoid arthritis

The efficacy of Leflunomide tablets in the treatment of rheumatoid arthritis was demonstrated in 4 controlled trials (1 in phase II and 3 in phase III). The phase II trial, study YU203, randomised 402 subjects with active rheumatoid arthritis to placebo (n=102), leflunomide 5 mg (n=95), 10 mg (n=101) or 25 mg/day (n=104). The treatment duration was 6 months.

All leflunomide patients in the phase III trials used an initial dose of 100 mg for 3 days.

Study MN301 randomised 358 subjects with active rheumatoid arthritis to leflunomide 20 mg/day (n=133), sulphasalazine 2 g/day (n=133), or placebo (n=92). Treatment duration was 6 months. Study MN303 was an optional 6-month blinded continuation of MN301 without the placebo arm, resulting in a 12-month comparison of leflunomide and sulphasalazine.

Study MN302 randomised 999 subjects with active rheumatoid arthritis to leflunomide 20 mg/day (n=501) or methotrexate at 7.5 mg/week increasing to 15 mg/week (n=498). Folate supplementation was optional and only used in 10% of patients. Treatment duration was 12-months. Study US301 randomised 482 subjects with active rheumatoid arthritis to leflunomide 20 mg/day (n=182), methotrexate 7.5 mg/week increasing to 15 mg/week (n=182), or placebo (n=118). All patients received folate 1 mg bid. Treatment duration was 12 months.

Leflunomide at a daily dose of at least 10 mg (10 to 25 mg in study YU203, 20 mg in studies MN301 and US301) was statistically significantly superior to placebo in reducing the signs and symptoms of rheumatoid arthritis in all 3 placebo-controlled trials. The ACR (American College of Rheumatology) response rates in study YU203 were 27.7% for placebo, 31.9% for 5 mg, 50.5% for 10 mg and 54.5% for 25 mg/day. In the phase III trials, the ACR response rates for leflunomide 20 mg/day vs. placebo were 54.6% vs. 28.6% (study MN301), and 49.4% vs. 26.3% (study US301). After 12 months with active treatment, the ACR response rates in leflunomide patients were 52.3% (studies MN301/303), 50.5% (study MN302) and 49.4% (study US301), compared to 53.8% (studies MN301/303) in sulphasalazine patients, 64.8% (study MN302), and 43.9% (study US301) in methotrexate patients. In study MN302 leflunomide was significantly less effective than methotrexate. However, in study US301 no significant differences were observed between leflunomide and methotrexate in the primary efficacy parameters. No difference was observed between leflunomide and sulphasalazine (study MN301). The leflunomide treatment effect was evident by 1 month, stabilised by 3 to 6 months and continued throughout the course of treatment.

Paediatrics

Leflunomide was studied in a single multicenter, randomized, double-blind, active-controlled trial in 94 patients (47 per arm) with polyarticular course juvenile rheumatoid arthritis. Patients were 3–17 years of age with active polyarticular course JRA regardless of onset type and naive to methotrexate or leflunomide. In this trial, the loading dose and maintenance dose of leflunomide was based on three weight categories: <20 kg, 20-40 kg, and >40 kg. After 16 weeks treatment, the difference in response rates was statistically significant in favour of methotrexate at the JRA Definition of Improvement (DOI) ≥30% (p=0.02). In responders, this response was maintained during 48 weeks (see section 4.2).

Psoriatic arthritis

The efficacy of Leflunomide tablets was demonstrated in one controlled, randomised, double blind study 3L01 in 188 patients with psoriatic arthritis, treated at 20 mg/day. Treatment duration was 6 months.
Leflunomide 20 mg/day was significantly superior to placebo in reducing the symptoms of arthritis in patients with psoriatic arthritis: the PsARC (Psoriatic Arthritis treatment Response Criteria) responders were 59% in the leflunomide group and 29.7% in the placebo group by 6 months (p<0.0001). The effect of leflunomide on improvement of function and on reduction of skin lesions was modest.

5.2 Pharmacokinetic properties

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 14C-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 \textit{in vivo} activity of Leflunomide tablets.

\textit{Absorption}

Excretion data from the 14C 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. 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. 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.

\textit{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. \textit{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.

\textit{Metabolism}

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 occur in microsomal and cytosolic cellular fractions. Interaction studies with cimetidine (non-specific cytochrome P450 inhibitor) and rifampicin (non-specific cytochrome P450 inducer), indicate that \textit{in vivo} CYP enzymes are involved in the metabolism of leflunomide only to a small extent.

\textit{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.
Pharmacokinetics in renal failure

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.

Pharmacokinetics in liver failure

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.

Pharmacokinetics in paediatrics

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).

Pharmacokinetics in elderly

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

*Tablet core:*
- Cellulose microcrystalline
- Pregelatinized starch (maize starch 1500)
- Povidone (E1201) (K30)
- Crospovidone (E1202) (Type A)
- Silica colloidal anhydrous
- Magnesium stearate (E470b)
- Lactose monohydrate

*Film-coating:*
- Opadry OY-SR-6497 in the 20mg
[Consisting of: Hypermellose 15cP (E464), Titanium dioxide (E171), Macrogol 6000, Talc, Iron oxide yellow (E172)]

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.
Once opened: 30 days

6.4 Special precautions for storage
Bottle: Keep the container tightly closed.

6.5 Nature and contents of container
Bottle: 30 ml white HDPE container, with tamper-evident closure with an integrated desiccant or desiccant sachet, containing 30 film-coated tablets, respectively.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Aspire Pharma Ltd
Antrobus House Business Centre
18 College Street
Petersfield
Hampshire
GU31 4AD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 35533/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/06/2011

10 DATE OF REVISION OF THE TEXT
17/06/2011
Module 3

PAR Leflunomide 10 mg & 20 mg film-coated tablets

Module 3

1. WHAT LEFLUNOMIDE IS AND WHAT IT IS USED FOR

Leflunomide belongs to a group of medicines called anti-rheumatic medicines. Leflunomide is used to treat adult patients with active rheumatoid arthritis or with active psoriatic arthritis. Symptoms of rheumatoid arthritis include inflammation of joints, swelling, difficulty moving and pain. Other symptoms that affect the entire body include loss of appetite, fever, loss of energy and anaemia (loss of red blood cells). Symptoms of active psoriatic arthritis include inflammation of joints, swelling, difficulty moving, pain and patches of red, scaly skin (skin lesions).

2. BEFORE YOU TAKE LEFLUNOMIDE

Do not take Leflunomide
- If you have ever had an allergic reaction to leflunomide (especially a serious skin reaction, often accompanied by fever, joint pain, red skin blisters or blisters, etc.), Stevens-Johnson syndrome or any of the other ingredients of Leflunomide.
- If you have any liver problems.
- If you have moderate to severe kidney problems.
- If you have severely low numbers of proteins in your blood (hypothyroidism).
- If you suffer from any problem which affects your immune system (e.g., AIDS).
- If you have any problem with your bone marrow, or if you have low numbers of red or white cells in your blood or a reduced number of platelets.
- If you are suffering from a serious infection.
- If you are pregnant or breast-feeding.

Take special care with Leflunomide
- If you have ever suffered from tuberculosis (a lung disease).
- If you are a male and wish to father a child, as Leflunomide can cause birth defects in new-born infants. To minimise any possible risk, men wishing to father a child should contact their doctor who may advise you to stop taking Leflunomide and take certain medicines to stop the release of Leflunomide from your body. You will then need a blood test to make sure that Leflunomide has been sufficiently removed from your body, and you should then wait for at least another 3 months.
- Leflunomide can occasionally cause some problems with your blood, liver or lungs. It may also cause some serious allergic reactions, or increase the chance of a severe infection. For more information on these, please read section 4 (possible side-effects).

Your doctor will carry out blood tests at regular intervals, before and during treatment with Leflunomide, to monitor your blood cells and liver. Your doctor will also check your blood pressure regularly as Leflunomide can cause an increase in blood pressure.

Leflunomide is not recommended for use in children and adolescents below 18 years of age.

Taking other medicines
- Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is especially important if you are taking:
  - other medicines for rheumatoid arthritis such as antimalarials (e.g., chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive drugs (e.g., methotrexate) as these combinations are not advisable.
  - a medicine called celecoxib (used to reduce high cholesterol) or activated charcoal as these medicines can reduce the amount of Leflunomide which is absorbed by the body.
  - phenytoin (used to treat epilepsy), Warfarin or fenproc我心里 (used to thin the blood) or tolbutamide (used to treat type 2 diabetes) as these medicines may increase the risk of side effects.
  - If you are already taking a non-steroidal anti-inflammatory drug (NSAID) and/or corticosteroids, you may continue to take them after starting Leflunomide.

Vaccinations
- If you have to be vaccinated, ask your doctor for advice. Certain vaccinations should not be given while taking Leflunomide, and for a certain amount of time after stopping treatment.

Taking Leflunomide with food and drink
- Leflunomide may be taken with or without food.
- It is not recommended to drink alcohol during treatment with Leflunomide. Drinking alcohol while taking Leflunomide may increase the chance of liver damage.

Pregnancy and breast-feeding
- Do not take Leflunomide if you are pregnant or think you may be pregnant. Women of childbearing potential must not take Leflunomide without using reliable contraceptive measures. Tell your doctor if you plan to become pregnant after stopping treatment with Leflunomide, as you need to ensure that all traces of Leflunomide have left your body before you become pregnant. This may take up to 2 years. This may be reduced to a few weeks by taking certain medicines which speed up removal of leflunomide from your body.
- In either case, it should be confirmed by a blood test that Leflunomide has been sufficiently removed from your body and you should then wait for at least another month before you become pregnant.
- For further information on the laboratory testing please contact your doctor.
- If you suspect that you are pregnant while taking Leflunomide or in the two years after you have stopped treatment, you must contact your doctor immediately for a pregnancy test. If the test confirms that you are pregnant, your doctor may suggest treatment with other medicines to speed up the removal of Leflunomide from the body, as this may decrease the risk to your baby.

Driving and using machines
- Leflunomide can make you feel dizzy which may impair your ability to concentrate and react. If you are affected, do not drive or use machines.

Important information about some of the ingredients of Leflunomide
- Leflunomide contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE LEFLUNOMIDE

Always take Leflunomide exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
- The usual starting dosage of Leflunomide is 100 mg once daily for the first three days. After this, most patients need a dose of:
  - For rheumatoid arthritis: 10 or 20 mg Leflunomide once daily, depending on the severity of the disease.
  - For psoriatic arthritis: 20 mg Leflunomide once daily.

Swallow the tablet whole and with plenty of water.
- It may take about 4 weeks or longer until you start to feel an improvement in your condition. Some patients may even still...
feel further improvements after 4 to 6 months of therapy. You will normally take Leflunomide over long periods of time.

If you take more Leflunomide than you should
If you take more Leflunomide than you should, contact your doctor or other medical advice. If possible, take your tablets or the box with you to show the doctor.

If you forget to take Leflunomide
If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, leflunomide can cause side effects, although not everybody gets them.

Tell your doctor immediately and stop taking leflunomide:
- if you experience weakness, feel light-headed or dizzy or have difficulty breathing, as these may be signs of a serious allergic reaction,
- if you develop a skin rash or ulcers in your mouth, as these may indicate severe, sometimes life-threatening reactions (e.g. Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme).

Tell your doctor immediately if you experience:
- pale skin, tiredness, or bruising
- these may indicate blood disorders caused by an imbalance in the different types of blood cells which make up blood,
- tiredness, abdominal pain, or jaundice (yellow discoloration of the eyes or skin), as these may indicate serious conditions such as liver failure, which may be fatal,
- any symptoms of an infection such as fever, sore throat or cough, as leflunomide may increase the chance of a severe infection which may be life-threatening.
- a cough or breathing problems as these may indicate inflammation of the lung (interstitial lung disease).

Common side effects (affects 1 to 10 users in 100)
- a slight decrease in the number of white blood cells (leucopenia),
- mild allergic reactions,
- loss of appetite, weight loss (usually insignificant),
- tiredness (asthenia),
- headache, dizziness,
- abnormal skin sensations like tingling (paraesthesia),
- mild increase in blood pressure,
- diarrhoea,
- nausea, vomiting,
- inflammation of the mouth or mouth ulcers,
- abdominal pain,
- an increase in some liver test results,
- increased hair loss,
- eczema, dry skin, rash, itching,
- tendinitis (pain caused by inflammation in the membrane surrounding the tendons usually in the foot or hands),
- an increase of certain enzymes in the blood (creatine phosphokinase).

Uncommon side effects (affects 1 to 10 users in 1,000)
- a decrease in the number of red blood cells (anaemia) and a decrease in the number of blood platelets (thrombocytopenia),
- a decrease in the levels of potassium in the blood,
- anxiety,
- taste disturbances,
- urticaria (nettle rash),
- tendinopathy, an increase in the levels of fat in the blood (cholesterol and triglycerides),
- a decrease in the levels of phosphate in the blood.

Rare side effects (affects 1 to 10 users in 10,000)
- an increase in the numbers of blood cells called eosinophils (eosinophilia), mild decrease in the number of white blood cells (leucopenia), decrease in the number of all blood cells (pancytopenia),
- severe increase in blood pressure,
- inflammation of the lung (interstitial lung disease),
- an increase in some liver results which may develop into serious conditions such as hepatitis and jaundice,
- severe infections called sepsis which may be fatal,
- an increase of certain enzymes in the blood (lactate dehydrogenase).

Very rare side effects (affects less than 1 user in 10,000)
- a marked decrease of some white blood cells (agranulocytosis),
- severe and potentially severe allergic reactions,
- inflammation of the small vessels (vasculitis, including cutaneous necrotizing vasculitis),
- problems in the nerves of the arms or legs (peripheral neuropathy),
- inflammation of the pancreas (pancreatitis),
- severe liver injury such as liver failure or necrosis which may be fatal,
- severe sometimes life-threatening reactions (Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme).

Other side effects such as kidney failure, a decrease in the levels of uric acid in your blood, and male infertility (which is reversible if treatment with leflunomide is stopped) may also occur with a low but not known frequency.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE LEFLUNOMIDE

Keep out of the reach of children.

Do not use leflunomide after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

Bottle: Keep in the container tightly closed.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Leflunomide contains
- The active substance is leflunomide. One film-coated tablet contains 10 or 20mg of leflunomide.
- The other ingredients are: Cellulose microcrystalline, pregelatinized starch (maize starch 1500), povidone (E1201) (E803), crospovidone (E1202) (type A), silica colloidal anhydrous, magnesium stearate (E471), and lactose monohydrate in the tablets core, as well as Opadry II White Op 04-28068 in the 10mg film-coating (consisting of: Titanium dioxide (E171), Lactose monohydrate, Hypermellose 15CP(E464), Macrogol/PEG 4000, Hypermellose 3CP (E464), Hypermellose 55CP (E464) or Opadry Op 04-85037 in the 20mg film-coating (consisting of: Hypermellose 15CP (E464), Titanium dioxide (E171), Macrogol 6000, Talc, iron oxide yellow (E172)).

What Leflunomide looks like and contents of the pack
- Leflunomide 10mg film-coated tablets are white, round biconvex tablets.
- Leflunomide 20mg film-coated tablets are yellow, round biconvex, with a scoreline on one side. The scoreline is for the purpose of identification only.

The tablets are packed in bottles of 30 tablets.

Marketing Authorisation Holder

Aspire Pharma Ltd
Antares House Business Centre
18 College Street
Petersfield
Hampshire
GU31 4AD
United Kingdom

Manufacturer

Pharmatext S.A.
Derenakivi 6
Pallini 15351
Athens Greece

Alternative manufacturer

Pharmatext International S.A
Industrial Park Saphe, Rodopi Prefecture, Block No 5, Rodopi 69300, Greece

This leaflet was last approved in 05/2011
Module 4
Labelling

Carton:

Container:

Leflunomide 10 mg film-coated tablets
Leflunomide

Each film-coated tablet contains 10 mg leflunomide.
30 film-coated tablets

Also contains lactose. See leaflet for further information.
Read the package leaflet before use. Oral use. Keep out of the reach and sight of children. After first opening use within 30 days. Keep the container tightly closed.

MA Holder:
Aspire Pharma Ltd
Petersfield
Hampshire
GU31 4AD
United Kingdom

POM
PL 35533/008 PA 16159/002/001 1010078.1.3
Lot:
Exp:
PAR Leflunomide 10 mg & 20 mg film-coated tablets UK/H/2957/001-2/DC

Carton:

Container:

Leflunomide 20mg film-coated tablets
Leflunomide

Also contains lactose. See leaflet for further information. Read the package leaflet before use. Oral use. Keep out of the reach and sight of children. After first opening use within 30 days. Keep the container tightly closed.

MA Holder: Aspire Pharma Ltd Antebus House 18 College Street Petersfield Hampshire GU31 4AD United Kingdom
POM PL 3553/0009 PA 2619/002/009 101079-11.1

Exp:
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Leflunomide 10 mg and 20 mg film-coated tablets (PL 35533/0008-9; UK/H/2957/001-2/DC) could be approved. These applications were submitted by the decentralised procedure, with the UK as Reference Member State (RMS) and Ireland as Concerned Member State (CMS).

The products are prescription-only medicines for the treatment of adult patients with:
- active rheumatoid arthritis as a ‘disease-modifying anti-rheumatic drug’ (DMARD)
- active psoriatic arthritis

Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.

Switching from leflunomide to another DMARD without following the washout procedure (see section 4.4 of the SmPC) may also increase the risk of serious adverse reactions even a long time after the switching.

These are applications submitted according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Arava 10mg and 20mg Film Coated Tablets, which were first authorised to Sanofi-Aventis Deutschland GmbH on 02 September 1999 by the Community (EU/1/99/118/001-004 10mg; EU/1/99/118/005-008 and EU/1/99/118/010 20mg).

Leflunomide is a disease-modifying anti-rheumatic agent with anti-proliferative properties (selective immunosuppressive agent ATC code: L04AA13). Leflunomide can be administered with food, since the extent of absorption is comparable in the fed and fasting state. Leflunomide is rapidly converted to the active metabolite, A771726, by first-pass metabolism in the gut wall and liver. A771726 inhibits the human enzyme dihydroorotate dehydrogenase (DHODH) and exhibits antiproliferative activity.

No new non-clinical studies were conducted, which is acceptable given that the products are intended to be generic medicinal products of originator products that have been licensed for over 10 years.

One bioequivalence study (single dose) was submitted to support this application, comparing a higher strength test product Leflunomide 100 mg film-coated tablets (Aspire Pharma Ltd) with the reference product Arava 100 mg Film Coated Tablets (Sanofi-Aventis, UK)

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were for products that are intended to be generic medicinal products of an originator product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 208) on 10 May 2011. After a subsequent national phase, the licences were granted in the UK on 17 June 2011.
### II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Leflunomide 10 mg film-coated tablets  
Leflunomide 20 mg film-coated tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Leflunomide</td>
</tr>
</tbody>
</table>
| Pharmacotherapeutic classification (ATC code)  | Selective immunosuppressive agents.  
(L04AA13)                                                                     |
| Pharmaceutical form and strength(s)           | 10 mg and 20 mg tablets                                                          |
| Reference numbers for the Mutual Recognition Procedure | UK/H/2957/001-2/DC |
| Reference Member State                        | United Kingdom                                                                  |
| Member States concerned                      | Ireland                                                                         |
| Marketing Authorisation Number(s)             | PL 35533/0008-9                                                                |
| Name and address of the authorisation holder  | Aspire Pharma Ltd, Antrobus House Business Centre  
18 College Street, Petersfield, Hampshire, GU31 4AD, UK. |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Leflunomide
Chemical name: 5-methyl-N-[4-(Trifluoromethyl)phenyl]Isoxazole-4-Carboxamide

Structure:

```
F2C
\|\|
N\(\text{CH}_3\)
```

Molecular formula: \(\text{C}_{12}\text{H}_{9}\text{F}_3\text{N}_2\text{O}_2\)
Molecular mass: 270.20
Appearance: Leflunomide is a white to almost white powder. It is practically insoluble in water, freely soluble in methanol and sparingly soluble in methylene chloride. Leflunomide does not contain any chiral centres, hence it does not have optical isomers. However during the synthesis of leflunomide, a side reaction gives rise to the 3-Methyl –N-[4-trifluoromethyl]phenyl]4-Isoxazole carboxamide which is appositional isomer.

Leflunomide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance leflunomide are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, pregelatinized starch (maize starch 1500), povidone (E1201) (k30), crospovidone (E1202) (Type A), colloidal anhydrous silica, magnesium stearate (E470b) and lactose monohydrate.

In addition:

- The 10 mg strength contains the film coating Opadry II White OY-LS-28908 [consisting of: titanium dioxide (E171), lactose monohydrate, hypromellose 15cP (E464), macrogol/PEG 4000, hypromellose 3cP (E464) and hypromellose 50cP (E464)]
- The 20 mg strength contains the film coating Opadry OY-SR-6497 [consisting of: hypromellose 15cP (E464), titanium dioxide (E171), macrogol 6000, talc, iron oxide yellow (E172)]
All excipients comply with their respective European Pharmacopoeia monographs with the exception of Opadry II White OY-LS-28908 and Opadry OY-SR-6497 (which are controlled to suitable in-house specifications). In addition, the specifications for Opadry II White OY-LS-28908 and Opadry OY-SR-6497 are in compliance with Directive 78/25/EC (concerning use of colouring agents in foodstuff). Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**

The objective of the development programme was to formulate tablets containing 10 mg and 20 mg leflunomide, which could be considered generic medicinal products of Arava Film-Coated Tablets (Sanofi-Aventis, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**

The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-Closure System**

All strengths of finished product are packaged in high density polyethylene (HDPE) containers with an integrated desiccant or dessicant sachet. Each pack contains 30 film-coated tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**

Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years for the unopened container, which reduces to 30 days once opened, with the special storage conditions ‘Keep the container tightly closed’.
Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA forms are satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of leflunomide are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with other products already on the market, they are not considered to increase the environmental risk. Thus, the applicant’s justification is accepted.

There are no objections to the approval of these products from a non-clinical viewpoint.
III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, balanced, single-dose, two treatment, parallel-group study to compare the pharmacokinetics of the test product Leflunomide 100 mg film-coated tablets versus the reference product Arava 100 mg Tablets (Sanofi-Aventis, UK) in healthy adult male volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 100 mg tablet administered with 240 ml of water after an overnight fast of 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 144 hours post dose.

Leflunomide is rapidly converted to the active metabolite A771726 which has a long elimination half life. Measurement of the metabolite A771726 for bioequivalence is appropriate.

The pharmacokinetic results for A771726 (the active metabolite of leflunomide) for the test product versus the reference product for the 100 mg strength are presented below (non-transformed values; arithmetic mean $t_{\text{max}}$ median, range):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$ ng/ml/h</th>
<th>$t_{\text{max}}$ h</th>
<th>$C_{\text{max}}$ ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>803164.28 ±127124.05</td>
<td>5.40 ±3.13</td>
<td>7922.51 ±1880.06</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>882175.88 ±882175.88</td>
<td>3.35 ±1.36</td>
<td>8895.53 ±1362.72</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>90.59 (84.59-97.03%)</td>
<td>-</td>
<td>86.89(80.01-94.36%)</td>
</tr>
</tbody>
</table>

$\text{AUC}_{0-t}$ area under the plasma concentration-time curve from time zero to t hours

$C_{\text{max}}$ maximum plasma concentration

$T_{\text{max}}$ time for maximum concentration

*ln-transformed values

The 90% confidence intervals for $\text{AUC}_{0-t}$ and $C_{\text{max}}$ were within the predefined acceptance range for the active metabolite A771726 for the test versus the reference products. Bioequivalence has been demonstrated between the test and the reference products for the 100 mg strength.

As the 10 mg and 20 mg strengths of the product meet the criteria for a biowaiver specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 rev 1), the results and conclusions of the bioequivalence study for the 100 mg strength can be extrapolated to the 10 mg and 20 mg strengths.

Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for these applications.

Efficacy

No new efficacy data were submitted and none were required for these applications.
Safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are acceptable. The SmPC for each strength is consistent with that for the respective originator product. The PIL is consistent with the SmPC and in line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The Risk Management Plan proposed by the applicant is acceptable.

The applicant has made a commitment to ensure that any changes to the safety profile of the reference medicinal product requiring changes to the Risk Management Plan or product information are implemented for the generic product in a timely fashion.

Conditions or restrictions regarding supply and use imposed on the Marketing Authorisation Holder (MAH)
Medicinal product subject to restricted medical prescription (Summary of Product Characteristics, section 4.2).

Conditions or restrictions with regard to the safe and effective use of the medicinal product
Prior to placing the product on the market, the Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use leflunomide are provided with a physician educational pack containing the following:

- The Summary of Product Characteristics
- Physician Leaflet
  The Physician Leaflet should contain the following key messages:
  - That there is a risk of severe liver injury and so regular measurement of ALT (SGPT) levels to monitor liver function is important. The information provided in the Physician Leaflet should provide information on dose reduction, discontinuation and washout procedures.
  - The identified risk of synergistic hepato- or haematotoxicity associated with combination therapy with another Disease-Modifying Antirheumatic Drug (e.g. methotrexate)
  - That there is a risk of teratogenicity and so pregnancy must be avoided until leflunomide plasma levels are at an appropriate level. Physicians and patients should be made aware that there is an ad-hoc advisory service available to provide information on leflunomide plasma level laboratory testing
- The risk of infections, including opportunistic infections, and the contraindication for use in immunocompromised patients.
- The need to counsel patients on important risks associated with leflunomide therapy and appropriate precautions when using the medicine.

**Conclusion**
There are no objections to the approval of these products from a clinical viewpoint.

**IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

**QUALITY**
The important quality characteristics of Leflunomide 10 mg and 20 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

**NON-CLINICAL**
No new non-clinical data were submitted and none are required for applications of this type.

**EFFICACY**
Bioequivalence has been demonstrated between the applicant’s Leflunomide 100 mg film-coated tablets and the respective reference product (Arava 100mg Tablets). As the 10 mg and 20 mg strengths of the product meet the biowaver criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98 rev 1), the results and conclusions of the bioequivalence study for the 100 mg strength can be extrapolated to the 10 mg and 20 mg strength products.

No new or unexpected safety concerns arose from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate.

**BENEFIT-RISK ASSESSMENT**
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s and the originator’s leflunomide products are interchangeable. Extensive clinical experience with leflunomide is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is considered to be positive.
# Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
