Public Assessment Report

Decentralised Procedure

LEFLUNOMIDE APOTEX 10 MG TABLETS
LEFLUNOMIDE APOTEX 20 MG TABLETS

Procedure No: UK/H/2625/001-2/DC

UK Licence No: PL 27583/0138-9

APOTEX EUROPE BV
LAY SUMMARY

On 04 October 2010, Belgium, Czech Republic, Spain, Hungary, Luxembourg, the Netherlands, and the UK agreed to grant Marketing Authorisations to Apotex Europe BV for the medicinal products Leflunomide Apotex 10 mg and 20 mg Tablets (PL 27583/0138-9; UK/H/2625/001-2/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 27 October 2010.

Leflunomide Apotex 10 mg and 20 mg Tablets are Prescription-Only Medicines (POM) used for the treatment in adults who have:

- active rheumatoid arthritis as a “disease-modifying anti-rheumatic drug” (DMARD)
- 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 Apotex 10 mg and 20 mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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Module 1

| **Product Name** | Leflunomide Apotex 10 mg Tablets  
Leflunomide Apotex 20 mg Tablets |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<tr>
<td><strong>Active Substances</strong></td>
<td>Leflunomide</td>
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<td><strong>Form</strong></td>
<td>Tablet</td>
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<td><strong>Strength</strong></td>
<td>10 mg and 20 mg tablets</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Apotex Europe BV, Darwinweg 20, 2333 CR Leiden, The Netherlands.</td>
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<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
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<td><strong>Concerned Member States (CMS)</strong></td>
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<td><strong>Timetable</strong></td>
<td>Day 210 – 04 October 2010</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Leflunomide Apotex 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg leflunomide.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White, round tablets, engraved ‘LE’ over ‘10’ on one side and ‘APO’ on the other side.

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 also 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 is 20 mg once daily for patients with psoriatic arthritis (see section 5.1).

The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.

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

Elderly population
No dosage adjustment is required in patients above 65 years of age.
**Paediatric population**
Leflunomide is not recommended for use in patients below 18 years. Efficacy and safety in juvenile rheumatoid arthritis (JRA) have not been established (see sections 5.1 and 5.2). No data are available for use in paediatric patients with psoriatic arthritis.

**Administration**
Leflunomide 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 impairment, 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 also section 4.6). Pregnancy must be excluded before start of treatment with leflunomide,
- breast-feeding women (see also 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. Co-medication 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 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 and any concomitant myelosuppressive medication 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 and any other possibly associated medication 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 medications 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 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.

4.6 Pregnancy and lactation

Pregnancy
The active metabolite of leflunomide, A771726 is suspected to cause serious birth defects when administered during pregnancy.

Leflunomide 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), not known (cannot be estimated from the available data).

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

<table>
<thead>
<tr>
<th>Infections and infestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare: severe infections, including sepsis which may be fatal</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Common:</th>
<th>Uncommon:</th>
<th>Rare:</th>
<th>Not known:</th>
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<tbody>
<tr>
<td></td>
<td>CPK increased</td>
<td>hypokalaemia, hyperlipidemia, hypophosphataemia</td>
<td>LDH increased</td>
<td>hypouricemia</td>
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### Psychiatric disorders

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<thead>
<tr>
<th>Category</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Uncommon: anxiety</td>
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</table>

### Nervous system disorders

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<th>Category</th>
<th>Common:</th>
<th>Very rare: peripheral neuropathy</th>
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<tbody>
<tr>
<td></td>
<td>paraesthesia, headache, dizziness</td>
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### Cardiac disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Common:</th>
<th>Rare:</th>
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<tbody>
<tr>
<td></td>
<td>mild increase in blood pressure</td>
<td>severe increase in blood pressure</td>
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### Respiratory, thoracic and mediastinal disorders

<table>
<thead>
<tr>
<th>Category</th>
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<tbody>
<tr>
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<td>interstitial lung disease (including interstitial pneumonitis), which may be fatal</td>
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</tbody>
</table>

### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Common:</th>
<th>Uncommon: taste disturbances</th>
<th>Very rare: pancreatitis</th>
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<tbody>
<tr>
<td></td>
<td>diarrhoea, nausea, vomiting, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain</td>
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### Hepatobiliary disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Common:</th>
<th>Rare:</th>
<th>Very rare:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>elevation of liver parameters (transaminases [especially ALT], less often gamma-GT, alkaline phosphatase, bilirubin)</td>
<td>hepatitis, jaundice/cholestasis</td>
<td>severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal</td>
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### Skin and subcutaneous tissue disorders

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<tbody>
<tr>
<td></td>
<td>increased hair loss, eczema, rash (including maculopapular rash), pruritus, dry skin</td>
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### Musculoskeletal and connective tissue disorders

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<th>Category</th>
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<th>Uncommon: tendon rupture</th>
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<td>tenosynovitis</td>
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### Renal and urinary disorders

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<th>Not known: renal failure</th>
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</table>

### Reproductive system and breast disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Common:</th>
<th>Not known: marginal (reversible) decreases in sperm concentration, total sperm count and rapid progressive motility</th>
</tr>
</thead>
</table>

### General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Category</th>
<th>Common:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>anorexia, weight loss (usually insignificant), asthenia</td>
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4.9 Overdose

Symptoms

There have been reports of chronic overdose in patients taking leflunomide at daily doses up to five times the recommended daily dose, and reports of acute overdose in adults and children. There were no adverse events reported in the majority of case reports of overdose. Adverse events consistent with the safety profile for leflunomide were: 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 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: <20kg, 20-40 kg, and >40kg. 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 was demonstrated in one controlled, randomised, double blind study 3L01 in 188 patients with psoriatic arthritis, treated at 20mg/day. Treatment duration was 6 months.

Leflunomide 20mg/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.

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...
PAR Leflunomide Apotex 10 mg and 20 mg Tablets

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 cytochrome P450 inhibitor) and rifampicin (non-specific cytochrome P450 inducer) indicate that in vivo CYP enzymes are involved in the metabolism of leflunomide only to a small extent.

Elimination
Elimination of A771726 is slow and characterised by an apparent clearance of about 31 ml/hr. The elimination half-life in patients is approximately 2 weeks. After administration of a radiolabelled dose of leflunomide, radioactivity was equally excreted in faeces, probably by biliary elimination, and in urine. A771726 was still detectable in urine and faeces 36 days after a single administration. The principal urinary metabolites were glucuronide products derived from leflunomide (mainly in 0 to 24 hour samples) and an oxanilic acid derivative of A771726. The principal faecal component was A771726.

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

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

Pharmacokinetics in paediatrics
The pharmacokinetics of A771726 following oral administration of leflunomide have been investigated in 73 paediatric 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 paediatric patients with body weights ≤40 kg have a reduced systemic exposure (measured by C₀) 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
Lactose, anhydrous
Crospovidone type B
Magnesium stearate
Silica colloidal, anhydrous

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
Cold formable (Alu/Alu) blister packs of 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Apotex Europe BV
Darwinweg 20
2333 CR Leiden
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)
PL 27583/0138

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/10/2010

10 DATE OF REVISION OF THE TEXT
27/10/2010
1 NAME OF THE MEDICINAL PRODUCT
Leflunomide Apotex 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 20 mg leflunomide.
Excipient: Anhydrous lactose. Each tablet contains 78.2 mg anhydrous lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White, arc triangular shaped tablets, engraved ‘LE’ over ‘20’ on one side and ‘APO’ on the other side.

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 also 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 is 20 mg once daily for patients with psoriatic arthritis (see section 5.1).

The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.

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

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

Paediatric population
Leflunomide is not recommended for use in patients below 18 years. Efficacy and safety in juvenile rheumatoid arthritis (JRA) have not been established (see sections 5.1 and 5.2). No data are available for use in paediatric patients with psoriatic arthritis.
Administration
Leflunomide 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 impairment, 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 also section 4.6). Pregnancy must be excluded before start of treatment with leflunomide,
• breast-feeding women (see also 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. Co-medication 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 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 and any concomitant myelosuppressive medication 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. hepat- 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 and any other possibly associated medication 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 medications 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 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.

4.6 Pregnancy and lactation

Pregnancy
The active metabolite of leflunomide, A771726 is suspected to cause serious birth defects when administered during pregnancy. Leflunomide 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.

<table>
<thead>
<tr>
<th>Infections and infestations</th>
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<tbody>
<tr>
<td>Rare: severe infections, including sepsis which may be fatal</td>
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</table>

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).

<table>
<thead>
<tr>
<th>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</th>
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<tbody>
<tr>
<td>The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some immunosuppressive agents.</td>
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</table>

<table>
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<tr>
<th>Blood and lymphatic system disorders</th>
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</thead>
<tbody>
<tr>
<td>Common: leucopenia (leucocytes &gt;2 G/l)</td>
</tr>
<tr>
<td>Uncommon: anaemia, mild thrombocytopenia (platelets &lt;100 G/l)</td>
</tr>
<tr>
<td>Rare: pancytopenia (probably by antiproliferative mechanism), leucopenia (leucocytes &lt;2 G/l), eosinophilia</td>
</tr>
<tr>
<td>Very rare: agranulocytosis</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Immune system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: mild allergic reactions</td>
</tr>
<tr>
<td>Very rare: severe anaphylactic/anaphylactoid reactions, vasculitis, including cutaneous necrotizing vasculitis</td>
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<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
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<tbody>
<tr>
<td>Common: CPK increased</td>
</tr>
<tr>
<td>Uncommon: hypokalaemia, hyperlipidemia, hypophosphataemia</td>
</tr>
<tr>
<td>Rare: LDH increased</td>
</tr>
<tr>
<td>Not known: hypouricemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon: anxiety</td>
</tr>
</tbody>
</table>
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 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 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: <20kg, 20-40 kg, and >40kg. 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 was demonstrated in one controlled, randomised, double blind study 3L01 in 188 patients with psoriatic arthritis, treated at 20mg/day. Treatment duration was 6 months.

Leflunomide 20mg/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.

**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
arthritus 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 cytochrome P450 inhibitor) and rifampicin (non-specific cytochrome P450 inducer) indicate that in vivo CYP enzymes are involved in the metabolism of leflunomide only to a small extent.

Elimination

Elimination of A771726 is slow and characterised by an apparent clearance of about 31 ml/hr. The elimination half-life in patients is approximately 2 weeks. After administration of a radiolabelled dose of leflunomide, radioactivity was equally excreted in faeces, probably by biliary elimination, and in urine. A771726 was still detectable in urine and faeces 36 days after a single administration. The principal urinary metabolites were glucuronide products derived from leflunomide (mainly in 0 to 24 hour samples) and an oxanilic acid derivative of A771726. The principal faecal component was A771726.

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

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 impairment

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

Pharmacokinetics in paediatrics

The pharmacokinetics of A771726 following oral administration of leflunomide have been investigated in 73 paediatric 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 paediatric patients with body weights ≤40 kg have a reduced systemic exposure (measured by C_{ss}) 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 pannypolyathropy 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 \textit{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 \textbf{PHARMACEUTICAL PARTICULARS}

6.1 \textbf{List of excipients}
Lactose, anhydrous
Crospovidone type B
Magnesium stearate
Silica colloidal, anhydrous

6.2 \textbf{Incompatibilities}
Not applicable.

6.3 \textbf{Shelf life}
3 years.

6.4 \textbf{Special precautions for storage}
Store below 25°C.

6.5 \textbf{Nature and contents of container}
Cold formable (Alu/Alu) blister packs of 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 \textbf{Special precautions for disposal}
No special requirements.

7 \textbf{MARKETING AUTHORITY}
Apotex Europe BV
Darwinweg 20
2333 CR Leiden
The Netherlands

8 \textbf{MARKETING AUTHORITY NUMBER(S)}
PL 27583/0139

9 \textbf{DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY}
27/10/2010

10 \textbf{DATE OF REVISION OF THE TEXT}
27/10/2010
PAR Leflunomide Apothe 10 mg and 20 mg Tablets

UK/H/2625/001-2/DC

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Leflunomide 10 mg tablets
Leflunomide 20 mg tablets

Leflunomide

Read all of this leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

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.

In this leaflet:
1. What Leflunomide is and what it is used for
2. Before you take Leflunomide
3. How to take Leflunomide
4. Possible side effects
5. How to store Leflunomide
6. Further information

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 adults who have:

- active rheumatoid arthritis as a disease-modifying antirheumatic drug (DMARD)
- active psoriatic arthritis

The symptoms of rheumatoid arthritis can be:

- swelling or inflammation of joints
- pain in your hands or difficulty in moving
- symptoms that affect the whole body, including loss of appetite, fever, loss of energy and anaemia (lack of red blood cells)

The symptoms of psoriatic arthritis can be:

- swelling or inflammation of your joints
- pain in your skin or difficulty in moving
- red or scaly skin (skin lesions)

2. Before you take Leflunomide

Do not take Leflunomide if:

- you are allergic (hypersensitive) to leflunomide or to any of the other ingredients in this medicine (listed in section 6) especially if you have had a skin reaction such as blisters known as Stevens-Johnson syndrome
- you have liver problems
- you have problems with your immune system such as AIDs
- you have a low level of white and red blood cells, low platelet count in your body or problems with your bone marrow
- you have any serious infections
- you have moderate to severe kidney problems
- you have low levels of protein (hypoproteinemia) in your body especially if you have a condition known as nephrotic syndrome
- you are pregnant, planning to become pregnant or a woman of childbearing potential not taking any contraception
- you are breast-feeding

Do not take the medicine if this applies to you. If you are not sure, talk to your doctor or pharmacist before taking Leflunomide.

Take special care with Leflunomide:

Check with your doctor or pharmacist before taking your medicine if:

- you are taking methotrexate. Your doctor will wait a few weeks before giving you Leflunomide
- you have liver problems and low levels of protein in your body
- you have allergies. Your doctor will regularly carry out blood tests to ensure you have the right levels of red blood cells in your body
- you have skin infections or severe infections
- you have tuberculosis as this may develop again
- you have breathing problems
- you are a man and wish to become a father. Leflunomide may cause birth defects in new born infants. To reduce the risk your doctor may decide to stop giving you Leflunomide and give you medicines to remove Leflunomide from your body. Your doctor will carry out a blood test to make sure Leflunomide has been removed from your body. You should then wait at least 3 months

Tell your doctor if you get any of the following while taking the medicine:

- feeling weak, light-headed or dizzy
- skin rash or ulcers in your mouth
- pale skin, tiredness or bruising
- abdominal pain, or swelling of the eyes or skin (jaundice)
- infection such as fever, sore throat or cough
- problems breathing

If you get any of the above, tell your doctor.

Tests

Your doctor will regularly carry out blood tests before and during treatment with Leflunomide to monitor your blood cells and liver. Your doctor will also regularly check your blood pressure as Leflunomide may cause high blood pressure (hypertension).

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.

It is especially important to tell your doctor or pharmacist if you are taking any of the following medicines:

- medicines for rheumatoid arthritis such as antimalarials (e.g. chloroquine and hydroxychloroquine), methotrexate, intra-articular or oral prednisolone and other immunosuppressive drugs (e.g. methotrexate). These combinations are not advisable.
- medicines such as ciclosporin (for high cholesterol) or activated charcoal. These medicines can reduce the amount of Leflunomide absorbed by the body.
- medicines for epilepsy such as phenytoin.
- medicines to thin your blood such as warfarin or phenprocoumon
- medicines for type 2 diabetes such as tolbutamide
- vaccinations. Ask your doctor for advice. Certain vaccinations should not be given while taking Leflunomide, and for a certain amount of time after stopping it.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Leflunomide.

If you are already taking an anti-diabetic anti-inflammatory drug (RAID) and/or corticosteroids, you may continue to take them after starting Leflunomide.

Taking Leflunomide with food and drink

Leflunomide can be taken with or without food.

Do not drink alcohol while taking Leflunomide.

Pregnancy and breast-feeding

Do not take Leflunomide if you are pregnant or think you are pregnant. Women of child-bearing potential must not take Leflunomide without using reliable contraceptives 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 trying to 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.

Your doctor will give you a blood test to make sure that Leflunomide has been sufficiently removed from your body. You should then wait for at least another month before you become pregnant.

If you think 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 give you certain medicines to speed up the removal of Leflunomide from the body, as this may decrease the risk to your unborn baby.

Do not take Leflunomide if you are breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Leflunomide may cause dizziness. Do not drive or use any tools or machines until you know how Leflunomide affects you. Ask your doctor or pharmacist if you are unsure.

Important information about some of the ingredients of Leflunomide

Leflunomide contains benzyl alcohol. 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.

Taking the medicine

Swallow the tablets whole with a drink of water.

It may take about 4 weeks or longer before you start to feel an improvement in your condition. Some patients may even still feel further improvements after 4 to 6 months of treatment.

You will normally take Leflunomide over long periods of time.

How much medicine to take

- The usual dose is 100 mg each day for the first three days. After this your doctor will adjust your dose depending on your symptoms.
- For rheumatoid arthritis your doctor may adjust your dose to 10 mg or 20 mg to be taken once each day.
- For psoriatic arthritis your doctor may give you 20 mg to be taken once each day.

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Use in children
Leflunomide should not be taken by children or young people under the age of 18.

If you take more Leflunomide than you should
If you take more Leflunomide than you should, immediately contact your doctor or pharmacist.

- Take the medicine pack with you.

If you forget to take Leflunomide
- If you forget to take a dose of this medicine, take it as soon as you remember.
- However, if it is nearly time for the next dose, skip the missed 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 medicine, ask your doctor or pharmacist.

4. Possible Side effects

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

Stop taking Leflunomide and tell your doctor immediately if you experience any of the following while taking the medicine:

- Feeling sick, light-headed or dizzy or have difficulty breathing, as these may be signs of a serious allergic reaction.
- Stomach or bowel ulcers in your mouth, as these may cause severe, sometimes lifethreatening infections (e.g. severe infection or cancer).
- Malignant skin reactions (e.g. erythema multiforme)

Tell your doctor immediately if you experience:

- Pus, sores, toothache, or trouble brushing your teeth, as these may indicate blood disorders caused by an infection in the different types of blood cells which make up blood.
- Abnormal pain or yellowing of the eyes or skin (jaundice), as these may indicate serious conditions such as liver failure, which may be fatal.
- Symptoms of infection such as fever, sore throat or cough. Leflunomide may increase the chance of severe infection which may be life-threatening.
- Problems breathing as this may indicate inflammation of the lung (interstitial lung disease).

Common (affects less than 1 in 10 people):

- Night sweats, increased in the white blood cells (leukopenia).
- Mild allergic reactions.
- Loss of appetite or weight loss.
- Fatigue, constipation.
- Headache or feeling dizzy.
- Abnormal skin sensations including tingling (paresthesia).
- Mild increase in blood pressure.
- Blood in stool.
- Feeling sick (nausea) or being sick (vomiting).
- Inflammation of the mouth or mouth ulcers.
- Abnormal pupil.
- Increase in some liver function test results.
- Increased hair loss.
- Eczema, dry skin, rash.
- Puffiness caused by inflammation in the membrane surrounding the tendons usually in the feet or hands.
- Increase in certain enzymes in the blood e.g. creatinine phosphokinase (shown in blood tests).

Uncommon (affects less than 1 in 100 people):

- Increase in the number of red blood cells (anemia) or a decrease in the number of blood platelets (thrombocytopenia).
- Decrease in the levels of potassium in the blood.
- Gouty arthritis.
- Disturbances in taste.
- Urticaria (itchy rash).
- Numbness.
- Increase in the levels of fat in the blood (cholesterol and triglycerides).
- Decrease in the levels of phosphate in the blood.

Rare (affects less than 1 in 10,000 people):

- Increased in the numbers of blood cells called eosinophils (eosinophilia).
- Mild increase in the number of white blood cells (leukopenia).
- Decrease in the number of all blood cells (pancytopenia).
- Severe increase in blood pressure (hypertension).
- Inflammation of the lung (interstitial lung disease).
- Increase in liver test results which may develop into serious conditions such as hepatitis or jaundice.
- Severe infections known as sepsis which may be fatal.
- Increase of certain enzymes in the blood such as lactate dehydrogenase.

Very rare (affects less than 1 in 10,000 people):

- Marked decrease of some white blood cells (agranulocytosis).
- Severe allergic reactions.
- Infection of the small vessels (vasculitis, including cutaneous necrotising 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 and sometimes life-threatening reactions (Sjogren-Larsson syndrome, toxic epidermal necrolysis, erythema multiforme).

It is not known how many people will get the following:

- Milder skin reactions.
- Infections of the mouth.

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

5. How to store Leflunomide

- Keep out of the reach and sight of children.
- Store below 25°C.

Do not use Leflunomide after the expiry date which is stated on the carton and blister pack.

This expiry date refers to the last day of the month.

Medicines should not be disposed of via wastewater 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.

- Each Leflunomide 10 mg tablet contains 10 mg leflunomide.
- Each Leflunomide 20 mg tablet contains 20 mg leflunomide.

The other ingredients are anhydrous lactose, crospovidone type B, magnesium stearate and colloidal, amorphous silica.

What Leflunomide looks like and contents of the pack
- Leflunomide Apotex 10 mg tablets are white, round, engraved “LE” over “10” on one side and “10” on the other side.
- Leflunomide Apotex 20 mg tablets are white, arc triangular shaped, engraved “LE” over “20” on one side and “20” on the other side.
- The 10 mg and 20 mg tablets are available in blister packs of 30 and 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Apotex Europe BV, Europeweg 20, 2333 CR Leiden, The Netherlands
Manufacturer:
Apotex Nederland BV, Archimedesweg 2, 2333 CN Leiden, The Netherlands
Distributor: [To be completed nationally]

This leaflet was last approved in October 2019.
Module 4
Labelling

Carton:

Non varnish area

Area for lot/expiry imprint
Non varnish area

Braille area
Blister:
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 Apotex 10 mg and 20 mg Tablets (PL 27583/0138-9; UK/H/2625/001-2/DC) could be approved. These applications were submitted by the decentralised procedure, with the UK as Reference Member State (RMS), and Belgium, Czech Republic, Spain, Hungary, Luxembourg and the Netherlands as Concerned Member States (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.

Moreover, 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 for a long time after the switching.

These are applications made 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, 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 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 applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have 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 Practise (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 210) on 04 October 2010. After a subsequent national phase, the licences were granted in the UK on 27 October 2010.

### II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Leflunomide Apotex 10 mg Tablets  
Leflunomide Apotex 20 mg Tablets |
| Name(s) of the active substance(s) (INN) | Leflunomide |
| 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/2625/001-2/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Belgium, Czech Republic, Spain, Hungary, Luxembourg and The Netherlands. |
| Marketing Authorisation Number(s) | PL 27583/0138-9 |
| Name and address of the authorisation holder | Apotex Europe BV, Darwinweg 20, 2333 CR Leiden, the Netherlands. |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Leflunomide

Chemical name:

α,α,α-trifluoro-5-methyl-4-isoxazolecarboxy-p-toluidide;
5-methylisoxazole-4-carboxylic acid trifluoromethylanilide.
N-(4′-trifluoromethylphenyl)-5 methylisoxazole-4-caboxamide.

Structure:

Molecular formula: \( C_{12}H_9F_3N_2O_2 \)
Molecular mass: 270.20
Appearance: leflunomide is a white to almost white crystalline powder. It is soluble in methanol, ethanol, isopropanol, acetone, methylenechloride and dimethylsulfoxide. It is practically insoluble in water and aqueous buffers within the pH range 1.2 to 7.5. No stereoisomers exist for leflunomide as there are no asymmetric carbons in its structure. Three polymorphic forms are known for leflunomide.

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 anhydrous lactose, crospovidone type B, magnesium stearate and anhydrous silica colloidal.

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate and magnesium stearate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption. The supplier of the magnesium stearate has provided a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability, which covers all aspects of the manufacture and control of the excipient. The marketing authorisation holder has also confirmed that all future batches of finished product will use magnesium stearate sourced from vegetable origins.

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 safe, efficacious tablets, containing 10 mg and 20 mg leflunomide that could be considered generic medicinal products of Arava Film-Coated Tablets (Sanofi-Aventis GmbH).
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 finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and 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 aluminium/aluminium blisters, in pack sizes of 30 and 100 tablets.

The Marketing Authorisation Holder has stated that they do not intend to market all pack sizes of the products in all member states at this present time. However, they have committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

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 2 years for the 10 mg strength and 3 years for the 20 mg strength, with the special storage conditions ‘Store below 25°C’.

**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labels are pharmaceutically 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 pharmaceutically 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 products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As this product is intended for generic substitution with other products already on the market, it is 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, single-dose, one-period, three-way, parallel-group study to compare the pharmacokinetics of the test product Leflunomide Apotex 20mg Tablets versus the reference products Arava 20mg Tablets (Sanofi-Aventis, France and Australia) in healthy adult volunteers under fasted conditions.

All volunteers were dosed in a fasted state in three treatment periods. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The washout period (with cholestyramine administration) between treatment periods was at least 11 days. No values for AUC$_{0-\infty}$ were calculated due to the long half-life of A771726 and the truncated AUC$_{0-t}$.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>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>108362.0</td>
<td>2.56</td>
<td>2237.9</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>106907.8</td>
<td>2.71</td>
<td>2207.3</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>102 (91.0-113.0)</td>
<td>-</td>
<td>101 (88.5-115.0)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ ng/ml/h</th>
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<td>2237.9</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>116298.8</td>
<td>3.06</td>
<td>2374.4</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>92.8 (83.2-107.0)</td>
<td>-</td>
<td>94.1 (82.6-107.0)</td>
</tr>
</tbody>
</table>

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 AUC and $C_{\text{max}}$ were within the predefined acceptance range for the active metabolite A771726 for the test versus the Australian and French reference products. Thus, bioequivalence was demonstrated between the test and the French reference product, and the test and the Australian reference product. It has been confirmed that the French reference product used is qualitatively and quantitatively identical to the UK reference product. Thus, the test product and the UK can also be considered bioequivalent.

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

**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 raised by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPCs, PIL and labels are medically acceptable. The SmPC for each strength is consistent with that for its respective originator product. The PIL is consistent with the SmPC and in-line 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 applicant commits to submit, before marketing in any Member State, the required updated RMP addressing the safety concerns requiring risk minimisation activities and to adhere fully to the recommendations in EPAR / Arava® / emea-combined-h235 / AnnexIIB / Conditions of the marketing authorisation pertaining to safe and effective use of the medicinal product and other conditions pertaining to the RMP, with the exception of performing additional studies, but including additional pharmacovigilance activities as needed.

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 Apotex 10 mg and 20 mg 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 Apotex 20 mg Tablets and its respective reference product (Arava 20mg Tablets) As the 10mg strength of the product meets the biowaiver criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 20 mg strength can be extrapolated to the 10mg strength tablet.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products, 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 products and the originator products are interchangeable. Extensive clinical experience with leflunomide is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, 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>
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