SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

Rheumalef 10 film coated tablets

Rheumalef 20 film coated tablets

Rheumalef 100 film coated tablets

COMPOSITION:

Rheumalef 10:

Each 10 mg tablet contains 10 mg of leflunomide.

List of excipients: Colloidal silicon dioxide, crospovidone, hypromellose (3cP, 15cP and 50cP), macrogol/peg 4000, magnesium stearate, maize starch 1500, microcrystalline cellulose, povidone, titanium dioxide.

Contains sugar: Lactose monohydrate 19,20 mg

Rheumalef 20:

Each 20 mg tablet contains 20 mg of leflunomide.

List of excipients: Colloidal silicon dioxide, crospovidone, hypromellose (5cP), iron oxide yellow, macrogol/peg 6000, magnesium stearate, maize starch 1500, microcrystalline cellulose, povidone, talc, titanium dioxide.

Contains sugar: Lactose monohydrate 38,40 mg

Rheumalef 100:

Each 100 mg tablet contains 100 mg of leflunomide.

List of excipients: Colloidal silicon dioxide, crospovidone, hypromellose (3cP, 15cP and 50cP), macrogol/peg 4000, magnesium stearate, maize starch 1500, microcrystalline cellulose, povidone, titanium dioxide.

Contains sugar: Lactose monohydrate 192,0 mg

PHARMACOLOGICAL CLASSIFICATION:
A 3.1 Antirheumatoids (anti-inflammatory agents)

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Leflunomide is an isoxazole immunomodulatory agent which inhibits dihydroorotate dehydrogenase (an enzyme involved in de novo pyrimidine synthesis) and has antiproliferative activity. Several *in vivo* and *in vitro* experimental models have demonstrated an anti-inflammatory effect.

Pharmacokinetic properties:

After oral doses, leflunomide undergoes first-pass metabolism in the liver and gut wall to A-771726 (terrflunomide), the primary metabolite which is responsible for the majority of the in-vivo activity. The bioavailability of leflunomide after oral doses ranges from 82 to 95 %. Peak plasma concentrations of the active metabolite may occur from 1 to 24 hours after a single dose. A fatty meal has no significant impact on the plasma levels of the primary active metabolite. A-771726 is more than 99 % bound to plasma proteins, mainly albumin. It is further metabolised before elimination. About 43 % of a dose is eliminated in the urine, mainly as glucuronides and 48 % is eliminated in the faeces via the bile. A-771726 has an elimination half-life of about 2 weeks, which is thought to be mainly due to enterohepatic recycling. Cholestyramine or activated charcoal are able to interrupt recycling and can therefore accelerate leflunomide elimination.

INDICATIONS:

Rheumalef is indicated for the treatment of adult patients with:
Active rheumatoid arthritis as a “disease-modifying antirheumatic drug” (DMARD) and to improve physical function.

CONTRAINDICATIONS:

Rheumalef is contraindicated in:

- Patients with hypersensitivity to leflunomide (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients in **Rheumalef**.
- Patients with impairment of liver function.
- Patients with severe immunodeficiency states, e.g. AIDS.

- Patients with significantly impaired bone marrow function or significant anaemia, leukopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis.
- Patients with serious infections.
- Patients with moderate to severe renal insufficiency.
- Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome.
- Women who are pregnant or who are of childbearing potential and are not using reliable contraception during treatment with **Rheumalef** and thereafter as long as the plasma levels of the active metabolite are above 0,02 mg/ℓ. Pregnancy must be excluded before starting treatment with **Rheumalef**. Women must not breast-feed while they are receiving **Rheumalef**. (See **PREGNANCY AND LACTATION**.)
- Male patients should be aware of the possible male-mediated foetal toxicity. Reliable contraception during treatment with **Rheumalef** should also be guaranteed.

Rheumalef is not recommended for use in patients under 18 years.

WARNINGS and SPECIAL PRECAUTIONS:

Recent treatment with hepatotoxic or haematotoxic DMARDs may result in increased side effects; therefore, the initiation of **Rheumalef** treatment has to be carefully considered regarding these benefit / risk aspects. Furthermore, switching from **Rheumalef** to another DMARD without a washout period may increase the possibility of additive risks of side effects for a long time after the switching.
The active metabolite of **Rheumalef** has a long half-life, usually 1 to 4 weeks. Serious undesirable effects may occur (e.g. hepatotoxicity, haematotoxicity or allergic reactions - see below), even if the treatment with **Rheumalef** has been stopped. Therefore, when such toxicities occur or when switching to another DMARD (e.g. methotrexate) after treatment with **Rheumalef** or in case of a desired pregnancy, or if for any other reason the primary metabolite needs to be cleared rapidly from the body, a washout procedure should be performed (see ***washout procedures*** below). For washout procedures in case of desired pregnancy, refer to Pregnancy and Lactation.

Recommendations for monitoring and washout procedures:

Monitoring recommendations:

Rheumalef should be administered to patients only under careful medical supervision. ALT (SGPT)

must be checked before initiation of treatment and at least at monthly intervals during the first six months of treatment and every 6 – 8 weeks thereafter. For confirmed ALT (SGPT) elevations between 2 and 3 – fold the upper limit of normal, dose reduction from 20 mg to 10 mg may allow continuedadministration of **Rheumalef** under close monitoring. If ALT (SGPT) elevations between 2 and 3 – fold the upper limit of normal persist or if confirmed ALT elevations of more than 3 – fold the upper limit of normal are present, **Rheumalef** should be discontinued. Cholestyramine or activated charcoal should be administered to rapidly lower the levels of the active metabolite. Blood pressure must be checked before the start of **Rheumalef** treatment and periodically thereafter, as increases in blood pressure may occur. A complete blood cell count, including differential white blood cell count and platelets, must be performed before start of **Rheumalef** treatment as well as monthly for the first 6 months of treatment and every 6 – 8 weeks thereafter.

Combinations with other treatments:

The concomitant use of **Rheumalef** with antimalarials used in rheumatic diseases (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine, Tumor-Necrosis-Factor alpha inhibitors and other immunosuppressive agents (with the exception of methotrexate) has not been adequately studied. The risk associated with combination therapy, in particular in long-term treatment, is unknown. Since such therapy can lead to additive or even synergistic toxicity (e.g. hepato-or haematotoxicity), combination with another DMARD (e.g. methotrexate) is not advisable.

Switching to other treatments:

As **Rheumalef** has a long persistence in the body, switching to another DMARD (e.g. methotrexate) without a washout period may increase the possibility of additive risks (such as kinetic interaction, organ toxicity) even for a long time after the switching. Close monitoring of liver enzymes is recommended in the initial phase after switching. Similarly, recent treatment with hepatotoxic or haematotoxic medicines (e.g. methotrexate) may result in increased side effects; therefore, the initiation of **Rheumalef** treatment has to carefully be considered regarding these benefit / risk aspects.

Washout procedures:

Cholestyramine 8 g is administered 3 times daily. Alternatively, 50 g of activated powdered charcoal is administered 4 times daily, for a period of 11 days.

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

Liver reactions:
Since the active metabolite of leflunomide (the primary metabolite) is highly protein bound and cleared via hepatic metabolism and biliary secretion, plasma levels of the primary metabolite are expected to be increased in patients with hypoproteinaemia or impairment of liver function. **Rheumalef** is contraindicated in patients with severe hypoproteinaemia or impairment of liver function or pre-existing hepatic disease (refer to **CONTRAINDICATIONS**). Due to a potential for additive hepatotoxic effects, it is recommended that alcohol consumption be avoided during treatment with **Rheumalef**.

Haematological reactions:
In patients with pre-existing anaemia, leukopenia, 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 above) to reduce plasma levels of the primary metabolites should be considered.
Haematological monitoring (complete blood cell count, including differential white blood cell count and platelet count) should be performed frequently in:

- Patients with recent or concomitant treatment with immunosuppressive or haematotoxic medicines, and when **Rheumalef** treatment is followed by such substances without a washout period.
- Patients with a history of relevant haematological abnormalities.
- Patients with relevant haematological abnormalities at baseline due to causes other than rheumatoid arthritis.

In case of severe haematological reactions including pancytopenia, **Rheumalef** and any concomitant myelosuppresive medication must be discontinued and a **Rheumalef** washout procedures initiated.

Skin reactions:
In case of ulcerative stomatitis, **Rheumalef** administration should be discontinued. Cases of Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported in patients treated with **Rheumalef**. As soon as skin and / or mucosal reactions are observed which raise the suspicion of such severe reactions, **Rheumalef** and any other possibly associated medications must be discontinued, and a **Rheumalef** washout procedure initiated immediately. A complete washout is essential in such cases. In such cases re-exposure to **Rheumalef** is contraindicated (refer to **CONTRAINDICATIONS**).

Infections:

Medicinal products like **Rheumalef** with immunosuppressive potential, 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 stop **Rheumalef** treatment and administer a washout with cholestyramine as described above. The risk of tuberculosis should be considered. Patients with tuberculin reactivity must be carefully monitored because of the risk of tuberculosis reactivation.
Cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients receiving **Rheumalef** among other immunosuppressants.

Respiratory:

A potentially fatal disorder, interstitial lung disease, may occur acutely during therapy with **Rheumalef**. Patients should be warned to report pulmonary symptoms, such as cough and dyspnoea, which should be further investigated to exclude interstitial lung disease. If interstitial lung disease is suspected, **Rheumalef** should be discontinued and patients should be further investigated as appropriate.
It is recommended that patients with tuberculin reactivity be carefully monitored because of the risk of tuberculosis reactivation.

Renal impairment:

Presently, there is insufficient experience available to make specific dosage recommendations for patients with renal impairment. When administering **Rheumalef** in this population, caution must be exercised. Consideration must take into account that the active metabolite of **Rheumalef** is highly protein bound.

Peripheral neuropathy:

Peripheral neuropathy has been associated with leflunomide use. If a patient taking **Rheumalef** develops peripheral neuropathy, consider discontinuing **Rheumalef** treatment and perform the washout procedure (see ***washout procedures*** above).

Lactose Intolerance:
Rheumalef contains lactose. Patients with rare hereditary problems of galactose intolerance, the *Lapp* lactase deficiency, or glucose-galactose malabsorption should not take **Rheumalef**.

Effects on ability to drive and use machines:

Rheumalef may cause side effects such as dizziness, which may affect the patient's ability to concentrate and to react properly. Patients should therefore be advised not to drive or operate machinery until their individual susceptibility is known.

Recommendations for use in men:

Procreation:

To minimise any possible risk of male-mediated foetal toxicity, men wishing to father a child should consider discontinuing use of **Rheumalef** and taking cholestyramine 8 g, three times daily for 11 days. In either case the primary metabolite plasma concentration is then measured for the first time. Therefore, the primary metabolite 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.

INTERACTIONS:

Increased adverse effects may occur in case of recent or concomitant use of hepatotoxic (including alcohol), haematotoxic or immunosuppressive substances. This is also to be considered when **Rheumalef** treatment is followed by such substances without a washout period.

Phenytoin, tolbutamide, warfarin and many NSAIDs are metabolised by cytochrome P450 2C9 (CYP2C9). As the primary metabolite of **Rheumalef** inhibits CYP2C9, caution is advised when **Rheumalef** is given together with medicines, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin and tolbutamide. There have been case reports of increased prothrombin time, when leflunomide and warfarin were co-administered. Therefore, when **Rheumalef** is co-administered with warfarin, close INR (international normalised ratio) follow up and monitoring is recommended.

Following concomitant administration of a single dose of leflunomide to subjects receiving multiple doses of rifampicin (non-specific cytochrome P450 inducer), the peak levels of the primary metabolite

of leflunomide increased by approximately 40 %, whereas the AUC was not significantly changed. The mechanism of this effect is unclear. Because of the potential for **Rheumalef** levels to continually increase with multiple dosing, caution is advised if patients are to receive both **Rheumalef** and rifampicin.

Vaccination with live vaccines is not recommended. The long half-life of **Rheumalef** should be considered when contemplating administration of a live vaccine after stopping **Rheumalef**.

Administration of cholestyramine or activated charcoal leads to a rapid and significant decrease in plasma primary metabolite concentration. The mechanism is thought to be interruption of enterohepatic recycling and / or adsorption of the primary metabolite. **Rheumalef** should not be given to patients using cholestyramine.

PREGNANCY AND LACTATION:

Rheumalef is contraindicated in pregnancy and lactation.

Pregnancy:

The active metabolite of leflunomide is suspected to cause serious birth defects when administered during pregnancy. Pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with **Rheumalef** and for a certain period of time thereafter must not be given **Rheumalef**. Pregnancy must be ruled out before initiating treatment with **Rheumalef**.

Suspected pregnancy or women deciding to fall pregnant:

Patients must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the medical practitioner immediately for pregnancy testing, and if positive, the medical practitioner 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 medicine elimination washout procedure described below, at the first delay of menses, may decrease the risk of the foetus from **Rheumalef**.

Washout procedure: for women receiving **Rheumalef** treatment who wish to become pregnant, one of the following procedures is recommended:

- After discontinuing treatment with **Rheumalef**, cholestyramine 8 g is administered three times daily for a period of 11 days.

- After stopping treatment with **Rheumalef**, 50 g of activated charcoal is administered four times daily for a period of 11 days. The 11 days need not be consecutive unless there is a need to lower the primary metabolite plasma level rapidly. In either case, the primary metabolite plasma levels < 0,02 mg/ℓ must be verified by two separate tests at least 14 days apart. Human plasma levels of the active metabolite less than 0,02 mg/ℓ (0,02 µg/ml) are expected to have minimal risk based on available data. Without the medicine elimination procedures, it may take up to 2 years to reach the primary metabolite levels of <0,02 mg/ℓ, due to individual variation in medicine clearance. However, also after such a waiting period, verification of the primary metabolite levels of < 0,02 mg/ℓ by two separate tests at an interval of at least 14 days is required. If a waiting period of up to approximately 2 years under reliable contraception is considered impractical, prophylactic institution of a washout procedures may be advisable. Reliable contraception with oral contraceptives may not be guaranteed during the washout procedures with cholestyramine or activated charcoal. Use of alternative contraceptive methods is recommended.

Note: Both cholestyramine and activated charcoal may influence the absorption of oestrogens and progestogens such that the reliable contraception with oral contraceptives may not be guaranteed during the washout procedure with these agents. Use of alternate contraceptive methods is recommended.

Lactation

Breast-feeding women must not receive **Rheumalef**. Animal studies indicate that leflunomide or its metabolites are excreted into breast milk.

DOSAGE AND DIRECTIONS FOR USE:

Rheumalef treatment should be initiated by doctors experienced in the therapy of rheumatoid diseases. For monitoring recommendations refer to warnings and special precautions.

The initial dose of **Rheumalef** therapy is 100 mg once daily for 3 days.

The recommended maintenance dose is **Rheumalef** tablets 10 mg to 20 mg once daily. A therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months. In patients with

mild renal insufficiency no dosage adjustment is recommended. Patients above 65 years of age require no dosage adjustment.

Method of administration: Rheumalef tablet should be swallowed whole, with sufficient amounts of liquid. The extent of leflunomide absorption is not affected if it is taken with food.

SIDE EFFECTS:

The following side effects have been reported:

The most frequent adverse effects with **Rheumalef** 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, increased creatine phosphokinase (CPK) , anorexia, weight loss (usually insignificant), asthenia, mild allergic reactions and elevation of liver parameters (transaminases (especially ALT), less often gamma-GT, alkaline phosphatase, bilirubin)

Infections and infestations

Less frequent: severe infections, including sepsis which may be fatal.

Susceptibility to infections, including opportunistic infections. Thus, the overall incidence of infections can increase (in particular of rhinitis, bronchitis and pneumonia).

Neoplasms benign, malignant and unspecified (including cysts and polyps)

The risk of malignancy, particularly lymphoproliferative disorders, is increased.

Blood and lymphatic system disorders

Frequent: leucopenia (leucocytes > 2 G/l),

Less frequent: anaemia, mild thrombocytopenia (platelets < 100 G/l), pancytopenia (probably by antiproliferative mechanism), leucopenia (leucocytes < 2 G/l), eosinophilia, agranulocytosis. Recent, concomitant or consecutive use of potentially myelotoxic agents may be associated with a higher risk of haematological effects.

Immune system disorders

Frequent: allergic reactions

Less frequent: severe anaphylactic/anaphylactoid reactions, vasculitis, including cutaneous necrotising vasculitis

Metabolism and nutrition disorders

Frequent: increased creatine phosphokinase (CPK)

Less frequent: hypokalaemia, hyperlipidaemia, hypophosphataemia, increased LDH

Frequency Unknown: hypouricaemia

Psychiatric disorders

Less frequent: anxiety

Nervous system disorders

Frequent: paraesthesia, headache, dizziness

Less frequent: peripheral neuropathy

Cardiac disorders

Frequent: increase in blood pressure

Less frequent: severe increase in blood pressure

Respiratory, thoracic and mediastinal disorders

Less frequent: interstitial lung disease (including interstitial pneumonitis), which may be fatal

Gastrointestinal disorders

Frequent: diarrhoea, nausea, vomiting, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain

Less frequent: taste disturbances, pancreatitis

Hepatobiliary disorders

Frequent: elevation of liver parameters (transaminases [especially ALT], gamma-GT, alkaline phosphatase, bilirubin)

Less frequent: hepatitis, jaundice/cholestasis, severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal

Skin and subcutaneous tissue disorders

Frequent: increased hair loss, eczema, rash (including maculopapular rash), pruritus, dry skin

Less frequent: urticaria, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme

Not known: cutaneous lupus erythematosus, pustular psoriasis or worsening psoriasis.

Musculoskeletal and connective tissue disorders

Frequent: tenosynovitis

Less frequent: tendon rupture

Renal and urinary disorders

Frequency unknown: renal failure

Reproductive system and breast disorders

Frequency unknown: marginal (reversible) decreases in sperm concentration, total sperm count and rapid progressive motility

General disorders and administration site conditions

Frequent: anorexia, weight loss (usually insignificant), asthenia

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Adverse events occurring with overdose are consistent with the side effects profile for **Rheumalef**. In the event of relevant overdose or toxicity, cholestyramine or charcoal must be given to accelerate elimination. The washout procedures may be repeated if clinically necessary.

Rheumalef or its primary metabolite cannot be removed by haemodialysis or chronic ambulatory peritoneal dialysis (CAPD).

IDENTIFICATION:

Rheumalef 10 film coated tablets are white, round biconvex tablets.

Rheumalef 20 film coated tablets are yellow, round biconvex with a scoreline on one side of the

tablet.

Rheumalef 100 film coated tablets are white, oblong biconvex with a scoreline on one side of the tablet.

PRESENTATION:

Rheumalef 10 and Rheumalef 20 film coated tablets are packed in a white opaque polyethylene high density container, with a tamper-evident polypropylene cap, containing either 30 tablets in a 30 ml container or 100 tablets in a 40 ml container. Each HD Polyethylene container also contains a desiccant and is stored in an outer unit carton.

Rheumalef 10, 20 and 100 film coated tablets are packed in Aluminium foil/ PVC blisters of 3 or 10 tablets per blister, packed in strips of 1, 3 or 10 strips per outer unit carton.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Keep out of reach of children.

Store in outer container until before use.

Special precautions for storage

Blister: Store in the original package

Bottle: Keep the container tightly closed

REGISTRATION NUMBERS:

Rheumalef 10:	45/3.1/0404
Rheumalef 20:	45/3.1/0405
Rheumalef 100:	45/3.1/0406

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

ADCOCK INGRAM LIMITED

1 New Road

Erand Gardens

Midrand

1685

Gauteng, South Africa

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