PROPOSED PACKAGE INSERT

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

RAVALEF 10, film-coated tablets

RAVALEF 20, film-coated tablets

RAVALEF 100, film-coated tablets

COMPOSITION

RAVALEF 10: Each film-coated tablet contains 10 mg leflunomide

RAVALEF 20: Each film-coated tablet contains 20 mg leflunomide

RAVALEF 100: Each film-coated tablet contains 100 mg leflunomide

The inactive ingredients include: cellulose microcrystalline, crospovidone, lactose monohydrate, magnesium stearate, Opadry II White OY-LS-28908 (**RAVALEF 10**, **RAVALEF 100**), Opadry OY-SR-6497 (**RAVALEF 20**), pregelatinised starch, povidone and silica colloidal anhydrous.

Opadray II White OY-LS-28908 consisting of hypromellose, lactose monohydrate, macrogol and titanium dioxide.

Opadry OY-SR-6497 consisting of hypromellose, iron oxide yellow, macrogol, talc and titanium dioxide.

RAVALEF contains lactose monohydrate.

The active metabolite of RAVALEF 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 RAVALEF has been stopped. Therefore, when such toxicities occur or when switching to another DMARD (e.g. methotrexate) after treatment with RAVALEF in case of a desired pregnancy, or if for any other reason the primary metabolite needs to be cleared rapidly from the body, the washout procedure has to be followed. The procedure may be repeated as clinically necessary. Refer to PREGNANCY AND LACTATION for the washout procedure in case of desired pregnancy.

PHARMACOLOGICAL CLASSIFICATION

A 3.1 Antirheumatoids (anti-inflammatory agents)

PHARMACOLOGICAL ACTION

Pharmacodynamic properties: The active metabolite of leflunomide, inhibits the human enzyme dihydroorotate dehydrogenase and exhibits antiproliferative activity as well as an anti-inflammatory effect.

Pharmacokinetic properties: Leflunomide is converted to the active metabolite by first-pass metabolism (ring opening) in the gut wall and liver. The active metabolite is responsible for essentially all the *in vivo* activity of leflunomide.

Absorption: Excretion data from the ^{14}C study indicated that at least about 82 to 95 % of

the dose is absorbed. The time to peak plasma concentrations of the active metabolite 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 the active metabolite (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. 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 the active metabolite 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 the active metabolite and to the daily dose of leflunomide.
At a dose level of 20 mg/day, average plasma concentration of the active metabolite 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, the active metabolite is extensively bound to protein (albumin). The unbound fraction is about 0,62 %. Binding of the active metabolite is linear in the therapeutic concentration range. Binding of the active metabolite appears slightly reduced and more variable in plasma from patients with rheumatoid arthritis or chronic renal insufficiency.
The extensive protein binding could lead to displacement of other highly-bound medicines. Consistent with extensive protein binding the active metabolite has a low apparent volume of distribution (approximately 11 litres). There is no preferential uptake in erythrocytes.

Metabolism: Leflunomide is metabolised to one primary and many minor metabolites including TFMA (4-trifluoromethylaniline). The metabolic biotransformation of leflunomide to

the primary metabolite 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 the primary metabolite 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 is equally excreted in faeces, probably by biliary elimination, and in urine. The primary metabolite is still detectable in urine and faeces 36 days after a single administration.

It has been shown that administration of an oral suspension of activated powdered charcoal or cholestyramine leads to a rapid and significant increase in the primary metabolite's elimination rate and decline in plasma concentrations. 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 the active metabolite in CAPD subjects appeared to be similar to healthy volunteers. A more rapid elimination of the active metabolite was observed in haemodialysis subjects which was not due to extraction of medicine in the dialysate.

Pharmacokinetics in liver failure

No data are available regarding treatment of patients with hepatic impairment. The active

metabolite 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 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 Css) of the primary metabolite relative to adult rheumatoid arthritis patients.

Pharmacokinetics in elderly

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

INDICATIONS

RAVALEF is indicated for the treatment of adult patients with:

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

CONTRAINDICATIONS

- Hypersensitivity to leflunomide (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients of **RAVALEF**.
- Patients with impaired 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.
- Patients with moderate to severe renal insufficiency, because insufficient clinical experience is available in this patient group.
- Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome.
- Pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with **RAVALEF** and thereafter as long as the plasma levels of the active metabolite are above 0,02 mg/l. Pregnancy must be excluded before start of treatment with **RAVALEF**.
- Breastfeeding women.
- Patients under 18 years of age as safety and efficacy have not been studied in this age group.

WARNING and SPECIAL PRECAUTIONS

Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions. The initiation of **RAVALEF** treatment, therefore, has to be carefully considered regarding these benefit/risk aspects. Moreover, switching from **RAVALEF** to another DMARD without a washout period may also increase the risk of serious adverse reactions even for a long time after the switching.

The active metabolite of **RAVALEF** 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 **RAVALEF** has been stopped. Therefore, when such toxicities occur or when switching to another DMARD (e.g. methotrexate) after treatment with **RAVALEF** in case of a desired pregnancy, or if for any other reason the primary metabolite needs to be cleared rapidly from the body, the washout procedure has to be followed. The procedure may be repeated as clinically necessary. Refer to **PREGNANCY AND LACTATION** for the washout procedure in case of desired pregnancy.

Monitoring recommendations

RAVALEF should only be administered to patients under careful medical supervision. ALT 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.

Continued administration of **RAVALEF** under close monitoring for confirmed ALT elevations between 2- and 3-fold the upper limit of normal, dose reduction from 20 mg to 10 mg may be allowed.

Discontinue **RAVALEF** if ALT 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. Activated charcoal or cholestyramine should be administered to more rapidly lower the levels of the active metabolite.

Check the blood pressure before the start of **RAVALEF** treatment and periodically thereafter, as increases in blood pressure may occur.

Perform a complete blood cell count, including differential white blood cell count and platelets, before starting **RAVALEF** treatment as well as monthly for the first 6 months of treatment and every 6 – 8 weeks thereafter.

Combinations with other treatments

The use of **RAVALEF** with antimalarials used in rheumatic diseases (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive medicines has not been 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.

Caution is advised when **RAVALEF** is given together with medicines, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin and tolbutamide.

Switching to other treatments

As **RAVALEF** 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 medicines (e.g. methotrexate) may result in increased side effects; therefore, the initiation of **RAVALEF** treatment has to be carefully considered regarding these benefit/risk aspects and closer monitoring is recommended in the initial phase after switching.

Washout procedure

Cholestyramine 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.

Liver reactions

Cases of severe liver injury, including cases with fatal outcome, have been reported during treatment with **RAVALEF**. Most of the cases occur within the first 6 months of treatment. It is considered essential that monitoring recommendations are strictly adhered to.

ALT must be checked before initiation of **RAVALEF** 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 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 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, **RAVALEF** must be discontinued and washout procedures initiated. It is recommended that monitoring of liver enzymes be maintained after discontinuation of **RAVALEF** 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 **RAVALEF**.

Since the active metabolite of leflunomide 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. **RAVALEF** is contraindicated in patients with severe hypoproteinaemia or impairment of liver function (See **CONTRAINDICATIONS**).

Haematological reactions

Together with ALT, a complete blood cell count, including differential white blood cell count and platelets, must be performed before start of **RAVALEF** 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 side effects is increased. If such effects occur, a washout (see above) to reduce plasma levels of the primary metabolite should be considered.
In case of severe haematological reactions including pancytopenia, **RAVALEF** and any concomitant myelosuppressive medication must be discontinued and a leflunomide washout procedure initiated.

Skin reactions

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

Infections

It is known that medicines with immunosuppressive properties – like **RAVALEF** - 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 **RAVALEF** treatment and administer a washout procedure as described above.

Progressive Multifocal Leukoencephalopathy (PML) has been reported in patients receiving **RAVALEF** among other immunosuppressants.

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

Procreation (recommendations for men)

Male patients should be aware of the possible male-mediated foetal toxicity. Reliable contraception during treatment with **RAVALEF** should also be guaranteed.

There is 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 **RAVALEF** and taking cholestyramine 8 g, three times daily for 11 days or 50 g of activated powdered charcoal, four times daily for 11 days.

In either case the primary metabolite plasma concentration is then measured for the first time. Thereafter, 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.

Respiratory reactions

Interstitial lung disease has been reported during treatment with **RAVALEF**.

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 **RAVALEF** treatment and periodically thereafter.

Lactose

Contains lactose. Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **RAVALEF**.

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.

INTERACTIONS

Interactions studies have only been performed in adults.

Increased side effects may occur in case of recent or concomitant use of hepatotoxic or haematotoxic medicines or when **RAVALEF** treatment is followed by such medicines without a washout period. Therefore, closer monitoring of liver enzymes and haematological parameters is recommended in the initial phase after switching.

Co-administration of **RAVALEF** (10 to 20 mg per day) with methotrexate (10 to 25 mg per week) resulted in a 2- to 3-fold elevation in liver enzymes.

It is recommended that patients receiving **RAVALEF** are not treated with cholestyramine or activated powdered charcoal because this leads to a rapid and significant decrease in

primary metabolite plasma concentration. The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of the primary metabolite.

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

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 **RAVALEF** to patients receiving multiple doses of rifampicin (non-specific cytochrome P450 inducer) the primary metabolite 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 the primary metabolite inhibits cytochrome P450 2C9 (CYP2C9) activity. In clinical trials no safety problems were observed when **RAVALEF** and NSAIDs metabolised by CYP2C9 were co-administered. Caution is advised when **RAVALEF** is given together with medicines, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin, phenprocoumon and tolbutamide.

In vivo interactions studies have demonstrated that there is a lack of significant interaction between **RAVALEF** and triphasic oral contraceptives.

Vaccinations

No clinical data are available on the efficacy and safety of vaccinations during **RAVALEF** treatment. Vaccination with live attenuated vaccines is, however, not recommended. The

long half-life of **RAVALEF** should be considered when contemplating administration of a live attenuated vaccine after stopping **RAVALEF**.

PREGNANCY AND LACTATION

Pregnancy

The active metabolite of **RAVALEF**, is suspected to cause serious birth defects when administered during pregnancy. **RAVALEF** is contraindicated in pregnancy. Pregnancy must be excluded before start of treatment with **RAVALEF**.

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 medical practitioner immediately for pregnancy testing, and if positive, the doctor 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 procedure described below, at the first delay of menses may decrease the risk to the foetus from **RAVALEF**.

For women receiving **RAVALEF** 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 the primary metabolite (target concentration below 0,02 mg/l).

Waiting period

The primary metabolite 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 **RAVALEF**.

After a 2-year waiting period, the primary metabolite plasma concentration is measured for the first time. Thereafter, 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 no teratogenic risk is to be expected.

Washout procedure

After stopping treatment with **RAVALEF**:

- cholestyramine 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 cholestyramine 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 cholestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended.

Lactation

Animal studies indicate that leflunomide or its metabolites pass into breast milk. Breastfeeding women must, therefore, not take **RAVALEF**.

Fertility

Male patients to refer to **WARNINGS and SPECIAL PRECAUTIONS**.

DOSAGE AND DIRECTIONS FOR USE

The treatment should be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis.

Alanine aminotransferase (ALT) 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 **RAVALEF**,
- every two weeks during the first six months of treatment, and
- every 8 weeks thereafter.

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

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

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

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

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

Paediatric population

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

Administration

RAVALEF should be swallowed whole with sufficient amounts of liquid. The extent of **RAVALEF** absorption is not affected if it is taken with food.

SIDE EFFECTS

Infections and infestations

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

RAVALEF may increase 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 (incl. cysts and polyps)

The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of **RAVALEF**.

Blood and lymphatic system disorders

Frequent: leucopenia (leucocytes > 2 x 10^9/l / 2 G/l)

Less frequent: anaemia, mild thrombocytopenia (platelets < 100 x 10^9/l / 100 G/l), pancytopenia (probably by antiproliferative mechanism), leucopenia (leucocytes < 2 G/l), eosinophilia, agranulocytosis

Recent, concomitant or consecutive use of potentially myelotoxic medicines 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 CPK

Less frequent: hypokalaemia, hyperlipidaemia, hypophosphataemia, increased LDH

*Frequency unknow*n: hypouricaemia

Psychiatric disorders

Less frequent: anxiety

Nervous system disorders

Frequent: paraesthesia, headache, dizziness

Less frequent: peripheral neuropathy

Vascular 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], less often 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

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

Symptoms

Adverse events consistent with the safety profile for leflunomide are: abdominal pain, nausea, diarrhoea, elevated liver enzymes, anaemia, leucopenia, pruritus and rash.

Treatment

In the event of an overdose or toxicity, cholestyramine or charcoal is recommended to accelerate elimination. Cholestyramine given orally at a dose of 8 g three times a day for 24 hours to three healthy volunteers decreased plasma levels of the primary metabolite 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 by 37 % in 24 hours and by 48 % in 48 hours. These washout procedures may be repeated if clinically necessary.

Studies with both haemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that, the primary metabolite of **RAVALEF**, is not dialysable.

IDENTIFICATION

RAVALEF 10: White, round biconvex film-coated tablets.

RAVALEF 20: Yellow, round biconvex film-coated tablets with a scoreline on both sides.

RAVALEF 100: White, oblong biconvex film-coated tablets with a scoreline on one side.

PRESENTATION

RAVALEF 10 and **20** are packed in white opaque high density polyethylene (HDPE) containers as packs of 30's or 100's. Each container is sealed with a tamper-evident closure and contains a desiccant sachet. The containers are packed in cardboard cartons.

RAVALEF 10, 20 and **100** are also packed in blisters of OPA/ALU/PVC – Aluminium (Alu/Alu) foil. The blister strips are packed in cardboard cartons.

STORAGE INSTRUCTIONS

Store at or below 25 ˚C.

Store in original packaging.

Keep blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

RAVALEF 10: 46/3.1/0236

RAVALEF 20: 46/3.1/0237

RAVALEF 100: 46/3.1/0238

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

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