Professional Information

FINGOSOL 0.5

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINAL PRODUCT

FINGOSOL 0.5 capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0,5 mg fingolimod as hydrochloride.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

Size “3” hard gelatine capsule with a white opaque body and opaque yellow cap imprinted with “WF5” containing a white to off white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

FINGOSOL 0.5 is indicated for the following:

- The treatment of patients with relapsing forms of multiple sclerosis (MS), to reduce the frequency of relapses and to delay the progression of disability.

4.2. Posology and method of administration

Posology:

Do not exceed the recommended dosage.

The recommended dose of FINGOSOL 0.5 is one 0,5 mg capsule taken orally once daily. If a dose is missed, treatment should be continued with the next dose as planned.

On initiation of FINGOSOL 0.5 treatment, after the first dose, all patients should be observed, with hourly pulse and blood pressure measurement, for a period of at least 6 hours for signs and symptoms of bradycardia. All patients should have an electrocardiogram performed prior to dosing and at the end of 6-hour monitoring period (see section 4.4).

Special Populations

Dosage in Patients with Renal Impairments:

No dose adjustment of FINGOSOL 0.5 is needed in patients with renal impairment (see section 5.2).

Hepatic Insufficiency:

FINGOSOL 0.5 must not be used in patients with severe hepatic impairment (Child-Pugh class C) (see section 4.3). No dose adjustments are needed in patients with mild or moderate hepatic impairment.

Elderly patients:

FINGOSOL 0.5 should be used with caution in patients aged 65 years and over.

Diabetic patients:

FINGOSOL 0.5 should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular oedema (see section 4.4).

Paediatric Population

FINGOSOL 0.5 is not indicated for use children (see section 5.2).

Method of administration

FINGOSOL 0.5 should be taken orally, once daily with or without food (see section 5.2).

4.3. Contraindications

- Hypersensitivity to fingolimod or to any of the inactive ingredients of FINGOSOL 0.5 listed in section 6.1.
- Pregnancy and lactation (see section 4.6).
- Patients with severe cardiac dysrhythmias requiring antidysrhythmic medicines; Class 1a (e.g. quinidine, procainamide), Class III (e.g. amiodarone, sotalol) (see section 4.4).
- Known immunodeficiency syndrome.

- Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies).
- Severe active infections, active chronic infections (hepatitis, tuberculosis).
- Known active malignancies.
- Severe liver impairment (Child-Pugh class C).
- Patients with myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure in the previous 6 months.
- Patients with second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not wear a pacemaker (see section 4.4).
- Patients with a baseline QTc interval ≥ 500 ms (see section 4.4).

4.4. Special warnings and precautions for use

FINGOSOL 0.5 should be used only by neurologists experienced in the treatment of multiple sclerosis (MS).

FINGOSOL 0.5 induces a reduction in heart rate upon initiation of treatment, which can lead to bradydysrhythmia. The effect is usually maximal on Day 1, within the first 6 hours and heart rate normalises within 1 month. However, these events may occur at any time.

6-hour monitoring (ECG, heart rate and blood pressure) on Day 1 is mandatory for all patients, in order to determine individual response to treatment initiation. Patients who

experience these events or patients with risk factors should have extended monitoring (at least overnight).
If patients develop signs or symptoms related to heart rate reduction, the monitoring should be extended until resolution of the event.

Bradydysrhythmia

Initiation of FINGOSOL 0.5 treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays, including the occurrence of isolated reports of transient, spontaneously resolving complete AV block (see sections 4.8 and 5.1).

After the first dose, the decline in heart rate starts within one hour, and is maximal within 6 hours. This post-dose effect persists over the following days, although usually to a milder extent, and usually abates over the next weeks. With continued administration, the average heart rate returns towards baseline within one month. However individual patients may not return to baseline heart rate by the end of the first month. Conduction abnormalities were typically transient and asymptomatic. They usually did not require treatment and resolved within the first 24 hours on treatment. If necessary, the decrease in heart rate induced by fingolimod can be reversed by parenteral doses of atropine or isoprenaline.

All patients should have an ECG and blood pressure measurement performed prior to and 6 hours after the first dose of FINGOSOL 0.5. All patients should be monitored for a

period of 6 hours for signs and symptoms of bradycardia with hourly heart rate and blood pressure measurement. Continuous (real time) ECG monitoring during this 6-hour period is recommended.

Should post-dose bradydysrhythmia-related symptoms occur, appropriate clinical management should be initiated and monitoring should be continued until the symptoms have resolved. Should a patient require pharmacological intervention during the first-dose monitoring, overnight monitoring in a medical facility should be instituted and the first-dose monitoring should be repeated after the second dose of FINGOSOL 0.5.

If the heart rate at 6 hours is the lowest since the first dose was administered (suggesting that the maximum pharmacodynamic effect on the heart may not yet be manifest), monitoring should be extended by at least 2 hours and until heart rate increases again. Additionally, if after 6 hours, the heart rate is < 45 bpm, or the ECG shows new onset second degree or higher grade AV block or a QTc interval ≥ 500 ms, extended monitoring (at least overnight monitoring), should be performed, and until the findings have resolved. The occurrence at any time of third degree AV block should also lead to extended monitoring (at least overnight monitoring).

Very rare cases of T-wave inversion have been reported in patients treated with fingolimod. In case of T-wave inversion, the prescriber should ensure that there are no associated myocardial ischaemia signs or symptoms. If myocardial ischaemia is suspected, it is recommended to seek advice from a cardiologist.

Due to the risk of serious rhythm disturbances, FINGOSOL 0.5 should not be used in patients with sino-atrial heart block, a history of symptomatic bradycardia or recurrent syncope, or in patients with significant QT prolongation (QTc > 470 ms (female) or > 450 ms (male)). Since significant bradycardia may be poorly tolerated in patients with a history of cardiac arrest, uncontrolled hypertension or severe sleep apnoea, FINGOSOL 0.5 should not be used in these patients (see section 4.3). If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring, at least overnight extended monitoring is recommended for treatment initiation (see section 4.5).

FINGOSOL 0.5 has not been studied in patients with dysrhythmias requiring treatment with class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antidysrhythmic medicines. Class Ia and class III antidysrhythmic medicines have been associated with cases of Torsades de Pointes in patients with bradycardia. Since initiation of treatment results in decreased heart rate, FINGOSOL 0.5 should not be used concomitantly with these medicines.

Experience with FINGOSOL 0.5 is limited in patients receiving concurrent therapy with beta blockers, heart-rate-lowering calcium channel blockers (such as verapamil or diltiazem), or other substances which may decrease heart rate (e.g. ivabradine, digoxin, anticholinesteratic medicines or pilocarpine). Since the initiation of treatment is also associated with slowing of the heart rate (see section 4.8), concomitant use of these

substances during FINGOSOL 0.5 initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate treatment should not be initiated in patients who are concurrently treated with these substances (see section 4.5). If treatment with FINGOSOL 0.5 is considered, advice from a cardiologist should be sought regarding the switch to non-heartrate lowering medicines prior to initiation of treatment. If the heartrate lowering medication cannot be stopped, cardiologist's advice should be sought to determine appropriate first dose monitoring, at least overnight extended monitoring is recommended (see section 4.5).

The effects on heart rate and atrioventricular conduction may recur on re-introduction of treatment depending on duration of the interruption and time since start of treatment. The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for:

- 1 day or more during the first 2 weeks of treatment.
- more than 7 days during weeks 3 and 4 of treatment.
- more than 2 weeks after one month of treatment.

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.

QT interval

In a thorough QT interval study of doses of 1,25 or 2,5 mg fingolimod at steady-state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of QTcI, with the upper limit of the 90 % CI ≤ 13,0 ms. There

is no dose- or exposure-response relationship of fingolimod and QTcI prolongation. There is no consistent signal of increased incidence of QTcI outliers, either absolute or change from baseline, associated with fingolimod treatment.

The clinical relevance of this finding is unknown. In multiple sclerosis studies, clinically relevant effects on prolongation of the QTc-interval have not been observed but patients at risk for QT prolongation were not included in clinical studies.

Medicines that may prolong QTc interval are best avoided in patients with relevant risk factors, for example, hypokalaemia or congenital QT prolongation.

Immunosuppressive effects

FINGOSOL 0.5 has an immunosuppressive effect that predisposes patients to an infection risk, including opportunistic infections that can be fatal, and increases the risk of developing lymphomas and other malignancies, particularly those of the skin. Doctors should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the doctor.

Infections

FINGOSOL 0.5 causes a dose-dependent reduction in peripheral lymphocyte count to 20 % – 30 % of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues.

Before initiating treatment, a recent complete blood count (CBC) (i.e. within 6 months or after discontinuation of prior therapy) should be available. Assessments of CBC are also recommended periodically during treatment, at month 3 and at least yearly thereafter, and in case of signs of infection. Absolute lymphocyte count < 0,2 x 10^9/L, if confirmed, should lead to treatment interruption until recovery, because fingolimod treatment was interrupted in patients with absolute lymphocyte count < 0,2 x 10^9/L.

Initiation of treatment should be delayed in patients with severe active infection until resolution.

Patients need to be assessed for their immunity to varicella (chickenpox) prior to treatment. It is recommended that patients without a healthcare professional confirmed history of chickenpox or documentation of a full course of vaccination with varicella vaccine undergo antibody testing to varicella zoster virus (VZV) before initiating therapy. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment (see section 4.8). Initiation of treatment with should be postponed for 1 month to allow full effect of vaccination to occur.

The immune system effects of FINGOSOL 0.5 may increase the risk of infections, including opportunistic infections (see section 4.8). Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. When evaluating a patient with a suspected infection that could be serious, referral to a

doctor experienced in treating infections should be considered. During treatment, patients should be instructed to report promptly symptoms of infection to their doctor.

Suspension of treatment should be considered if a patient develops a serious infection.

Cases of cryptococcal meningitis (a fungal infection), sometimes fatal, have been reported in the post-marketing setting after approximately 2 - 3 years of treatment, although an exact relationship with the duration of treatment is unknown (see section 4.8). Patients with symptoms and signs consistent with cryptococcal meningitis (e.g. headache accompanied by mental changes such as confusion, hallucinations, and/or personality changes) should undergo prompt diagnostic evaluation. If cryptococcal meningitis is diagnosed, fingolimod should be suspended and appropriate treatment should be initiated. A multidisciplinary consultation (i.e. infectious disease specialist) should be undertaken if re-initiation of FINGOSOL 0.5 is essential.

Progressive multifocal leukoencephalopathy (PML) has been reported under fingolimod treatment (see section 4.8). PML is an opportunistic infection caused by John Cunningham virus (JCV), which may be fatal or result in severe disability. Cases of PML have occurred after approximately 2 - 3 years of monotherapy treatment without previous exposure to natalizumab, although an exact relationship with the duration of treatment is unknown. Additional PML cases have occurred in patients who had been treated previously with natalizumab, which has a known association with PML. PML can only occur in the presence of a JCV infection. If JCV testing is undertaken, it should be

considered that the influence of lymphopenia on the accuracy of anti-JCV antibody testing has not been studied in fingolimod-treated patients. It should also be noted that a negative anti-JCV antibody test does not preclude the possibility of subsequent JCV infection. Before initiating treatment with FINGOSOL 0.5, a baseline MRI should be available (usually within 3 months) as a reference. During routine MRI (in accordance with national and local recommendations), doctors should pay attention to PML suggestive lesions. MRI may be considered as part of increased vigilance in patients considered at increased risk of PML. If PML is suspected, MRI should be performed immediately for diagnostic purposes and treatment with fingolimod should be suspended until PML has been excluded.

Elimination of fingolimod following discontinuation of therapy may take up to two months and vigilance for infection should therefore be continued throughout this period. Patients should be instructed to report symptoms of infection up to 2 months after discontinuation of FINGOSOL 0.5**.**

Macular oedema

Macular oedema with or without visual symptoms has been reported in patients, occurring predominantly in the first 3 to 4 months of therapy. An ophthalmological evaluation is therefore recommended at 3 to 4 months after treatment initiation. If patients report visual disturbances at any time while FINGOSOL 0.5, evaluation of the fundus, including the macula, should be carried out.

Patients with history of uveitis and patients with diabetes mellitus are at increased risk of macular oedema (see section 4.8). FINGOSOL 0.5 has not been studied in multiple sclerosis patients with concomitant diabetes mellitus. It is recommended that multiple sclerosis patients with diabetes mellitus or a history of uveitis undergo an ophthalmological evaluation prior to initiating therapy and have follow-up evaluations while receiving therapy.

Continuation of FINGOSOL 0.5 in patients with macular oedema has not been evaluated. It is recommended that FINGOSOL 0.5 be discontinued if a patient develops macular oedema. A decision on whether FINGOSOL 0.5 therapy should be re-initiated after resolution of macular oedema needs to take into account the potential benefits and risks for the individual patient.

Liver function

Increased hepatic enzymes, in particular alanine aminotransaminase (ALT) but also gamma glutamyl transferase (GGT) and aspartate transaminase (AST) have been reported in multiple sclerosis patients. Elevations 3-fold the upper limit of normal (ULN) or greater in ALT occurred in patients treated with fingolimod 0,5 mg compared to placebo patients. Elevations 5-fold the ULN occurred in patients on fingolimod and patients on placebo. In clinical trials, fingolimod was discontinued if the elevation exceeded 5 times the ULN.

Recurrence of liver transaminase elevations occurred with rechallenge in some patients, supporting a relationship to fingolimod. Transaminase elevations occurred at any time

during treatment although the majority occurred within the first 12 months. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of FINGOSOL 0.5**.**

FINGOSOL 0.5 has not been studied in patients with severe pre-existing hepatic injury (Child-Pugh class C) and should not be used in these patients.

Due to the immunosuppressive properties of FINGOSOL 0.5, initiation of treatment should be delayed in patients with active viral hepatitis until resolution.

Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with FINGOSOL 0.5**.** In the absence of clinical symptoms, liver transaminases should be monitored at Months 1, 3, 6, 9 and 12 on therapy and periodically thereafter. If liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted, including serum bilirubin and alkaline phosphatase (ALP) measurement. With repeated confirmation of liver transaminases above 5 times the ULN, treatment with FINGOSOL 0.5 should be interrupted and only re-commenced once liver transaminase values have normalised.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have liver enzymes checked and FINGOSOL 0.5 should be discontinued if significant liver injury is confirmed (for example liver transaminase levels

greater than 5-fold the ULN and/or serum bilirubin elevations). Continuation of therapy will be dependent on whether another cause of liver injury is determined and on the benefits to patient of resuming therapy versus the risks of recurrence of liver dysfunction.

Although there are no data to establish that patients with pre-existing liver disease are at increased risk of developing elevated liver function tests when taking FINGOSOL 0.5**,** caution in the use of FINGOSOL 0.5 should be exercised in patients with a history of significant liver disease.

Interference with serological testing

Since FINGOSOL 0.5 reduces blood lymphocyte counts via re-distribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with FINGOSOL 0.5**.** Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes.

Blood pressure effects

Special care is indicated if patients with uncontrolled hypertension are treated with FINGOSOL 0.5**.**

Blood pressure should be regularly monitored during treatment with FINGOSOL 0.5**.**

Respiratory effects

Minor dose-dependent reductions in values for forced expiratory volume (FEV1) and diffusion capacity for carbon monoxide (DLCO) were observed with Fingolimod treatment starting in the first month of treatment and remaining stable thereafter. FINGOSOL 0.5 should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease.

Posterior reversible encephalopathy syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported with Fingolimod (see section 4.8). Symptoms reported included sudden onset of severe headache, nausea, vomiting, altered mental status, visual disturbances and seizure. Symptoms of PRES are usually reversible but may evolve into ischaemic stroke or cerebral haemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, FINGOSOL 0.5 should be discontinued.

Prior treatment with immunosuppressive or immunomodulatory therapies

There have been no studies performed to evaluate the efficacy and safety of FINGOSOL 0.5 when switching patients from teriflunomide, dimethyl fumarate or alemtuzumab treatment to FINGOSOL 0.5**.** When switching patients from another disease modifying therapy to FINGOSOL 0.5, the half-life and mode of action of the other therapy must be considered to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation. A CBC is recommended prior to initiating FINGOSOL 0.5 to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.

FINGOSOL 0.5 can generally be started immediately after discontinuation of interferon or glatiramer acetate.

For dimethyl fumarate, the washout period should be sufficient for CBC to recover before treatment with FINGOSOL 0.5 is started.

Due to the long half-life of natalizumab, elimination usually takes up to 2 – 3 months following discontinuation. Teriflunomide is also eliminated slowly from the plasma. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take from several months up to 2 years. An accelerated elimination procedure as defined in the teriflunomide summary of product characteristics is recommended or alternatively washout period should not be shorter than 3,5 months. Caution regarding potential concomitant immune effects is required when switching patients from natalizumab or teriflunomide to FINGOSOL 0.5.

Alemtuzumab has profound and prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with FINGOSOL 0.5 after alemtuzumab is not recommended unless the benefits of such treatment clearly outweigh the risks for the individual patient.

A decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration.

Co-administration with potent CYP450 inducers

The combination of FINGOSOL 0.5 with potent CYP450 inducers should be used with caution. Concomitant administration with St John's wort is not recommended (see section 4.5).

Cutaneous neoplasms

Basal cell carcinoma (BCC) and other cutaneous neoplasms, including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma, have been reported (see section 4.8). Vigilance for skin lesions is warranted and a medical evaluation of the skin is recommended at initiation, and then every 6 to 12 months taking into consideration clinical judgement. The patient should be referred to a dermatologist in case suspicious lesions are detected.

Since there is a potential risk of malignant skin growths, patients treated with FINGOSOL 0.5 should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

Stopping therapy

If a decision is made to stop treatment with FINGOSOL 0.5, a 6-week interval without therapy is needed, based on half-life, to clear fingolimod from the circulation (see section 5.2). Lymphocyte counts progressively return to normal range within 1 - 2 months of stopping therapy (see section 5.1). Starting other therapies during this

interval will result in concomitant exposure to fingolimod. Use of immunosuppressants soon after the discontinuation of FINGOSOL 0.5 may lead to an additive effect on the immune system and caution is therefore indicated.

4.5. Interaction with other medicines and other forms of interaction

Anti-neoplastic, immunomodulatory or immunosuppressive therapies

Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects.

Caution should also be exercised when switching patients from long-acting therapies with immune effects such as natalizumab, teriflunomide or mitoxantrone (see section 4.4). In multiple sclerosis clinical studies, the concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection.

Vaccination

During and for up to two months after treatment with FINGOSOL 0.5 vaccination may be less effective. The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided (see section 4.4 and 4.8).

Bradycardia-inducing substances

Fingolimod has been studied in combination with atenolol and diltiazem. When fingolimod was used with atenolol in an interaction study in healthy volunteers, there was an additional 15 % reduction of heart rate at fingolimod treatment initiation, an effect not seen with diltiazem. Treatment with FINGOSOL 0.5 should not be initiated in

patients receiving beta blockers, or other substances which may decrease heart rate, such as class Ia and III antidysrhythmics, calcium channel blockers (such as verapamil or diltiazem), ivabradine, digoxin, anticholinesteratic medicines or pilocarpine because of the potential additive effects on heart rate (see section 4.4 and 4.8). If treatment with FINGOSOL 0.5 is considered in such patients, advice from a cardiologist should be sought regarding the switch to non-heartrate lowering medicinal products or appropriate monitoring for treatment initiation, at least overnight monitoring is recommended, if the heart-rate-lowering medication cannot be stopped.

Pharmacokinetic interactions of other substances on fingolimod

Fingolimod is metabolised mainly by CYP4F2. Other enzymes like CYP3A4 may also contribute to its metabolism, notably in the case of strong induction of CYP3A4. Potent inhibitors of transporter proteins are not expected to influence fingolimod disposition. Co-administration of FINGOSOL 0.5 with ketoconazole resulted in a 1,7-fold increase in fingolimod and fingolimod phosphate exposure (AUC) by inhibition of CYP4F2. Caution should be exercised with substances that may inhibit CYP3A4 (protease inhibitors, azole antifungals, some macrolides such as clarithromycin or telithromycin).

Co-administration of carbamazepine 600 mg twice daily at steady-state and a single dose of fingolimod 2 mg reduced the AUC of fingolimod and its metabolite by approximately 40 %. Other strong CYP3A4 enzyme inducers, for example rifampicin, phenobarbital, phenytoin, efavirenz and St John's wort, may reduce the AUC of

fingolimod and its metabolite at least to this extent. As this could potentially impair the efficacy, their co-administration should be used with caution.
Concomitant administration with St John's wort is however not recommended (see section 4.4).

Pharmacokinetic interactions of fingolimod on other substances

FINGOSOL 0.5 is unlikely to interact with substances mainly cleared by the CYP450 enzymes or by substrates of the main transporter proteins.
Co-administration of FINGOSOL 0.5 with ciclosporin did not cause any change in the ciclosporin or fingolimod exposure.
Therefore, FINGOSOL 0.5 is not expected to alter the pharmacokinetics of medicinal products that are CYP3A4 substrates.

Co-administration of FINGOSOL 0.5 with oral contraceptives (ethinylestradiol and levonorgestrel) did not elicit any change in oral contraceptive exposure. No interaction studies have been performed with oral contraceptives containing other progestogens, however an effect of FINGOSOL 0.5 on their exposure is not expected.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Before initiation of FINGOSOL 0.5 treatment, women of childbearing potential should be counselled on the potential for serious risk to the foetus and the need for effective contraception during treatment with FINGOSOL 0.5. Since it takes approximately two

months to eliminate FINGOSOL 0.5 from the body on stopping treatment (see section 4.4), the potential risk to the foetus may persist and contraception should be continued during that period.

Available data do not suggest that FINGOSOL 0.5 would be associated with an increased risk of male-mediated foetal toxicity.

Pregnancy

Safety in pregnancy has not been established.

FINGOSOL 0.5 should not be used in pregnancy (see section 4.3).

Breastfeeding

Safety in lactation has not been established. FINGOSOL 0.5 should not be used in lactation (see section 4.3).

4.7. Effects on ability to drive and use machines

FINGOSOL 0.5 has no or negligible influence on the ability to drive and use machines. However, dizziness or drowsiness may occasionally occur when initiating therapy with FINGOSOL 0.5. On initiation of FINGOSOL 0.5 treatment, it is recommended that patients be observed for a period of 6 hours (see section 4.4).

4.8. Undesirable effects

Infections and infestations:

Frequent:	Influenza viral infections, bronchitis, sinusitis, gastroenteritis, herpes viral infections, tinea infections.
Less frequent:	Pneumonia.
Frequency unknown:	Progressive multifocal leukoencephalopathy (PML), cryptococcal infections.

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

Frequent:	Basal cell carcinoma.
Less frequent:	Malignant melanoma, lymphoma, squamous cell carcinoma, Kaposi's sarcoma.
Frequency unknown:	Merkel cell carcinoma.

Blood and the lymphatic system disorders:

Frequent:	Leucopenia, lymphopenia.
Less frequent:	Thrombocytopenia.
Frequency unknown:	Peripheral oedema.

Immune system disorders:

Frequency unknown:	Hypersensitivity reactions, including rash, urticaria and angioedema upon treatment initiation.

Psychiatric disorders:

Frequent:	Depression.

Less frequent: Depressed mood**.**

Nervous system disorders:

Frequent: Headache, dizziness, paraesthesia, migraine.

Less frequent: Posterior reversible encephalopathy syndrome (PRES).

Eye disorders:

Frequent: Eye pain, blurred vision.

Less frequent: Macular oedema.

Cardiac disorders:

Frequent: Bradycardia, atrioventricular (AV) block.

Less frequent: T-wave inversion.

Vascular disorders:

Frequent: Hypertension.

Respiratory, thoracic and mediastinal disorders:

Frequent: Cough, dyspnoea.

Gastrointestinal disorders:

Frequent: Diarrhoea.

Less frequent: Nausea.

Skin and subcutaneous tissue disorders:

Frequent:	Eczema, alopecia, pruritus.

Musculoskeletal, connective tissue disorders:

Frequent:	Back pain.

General disorders and administration site conditions:

Frequent:	Asthenia.

Investigations:

Frequent:	Increased hepatic enzymes (increased alanine transaminase (ALT), gamma glutamyl transferase (GGT), aspartate transaminase), increased blood triglycerides, decreased weight, abnormal liver function test.
Less frequent:	Decreased neutrophil count.

4.9. Overdose

At 40 mg (i.e. 80-fold above the recommended dose) administered to healthy volunteers, 5 of 6 subjects reported mild chest tightness or discomfort which was clinically consistent with bronchoconstriction.

FINGOSOL 0.5 can induce bradycardia. The decline in heart rate usually starts within one hour of the first dose and is maximal within 6 hours. There have been reports of slow atrioventricular conduction, with isolated reports of transient, spontaneously resolving complete AV block (see section 4.4 and 4.8).

If the overdose constitutes first exposure to FINGOSOL 0.5 it is important to observe patients for signs and symptoms of bradycardia, which could include overnight monitoring. Regular measurements of pulse rate and blood pressure are required and electrocardiograms should be performed (see section 4.2 and 4.4).

Neither dialysis nor plasma exchange would result in meaningful removal of FINGOSOL 0.5 from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 34 other, selective immunosuppressive agents

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants

ATC code: L04AA27

Mechanism of Action

Fingolimod is a sphingosine-1-phosphate receptor modulator. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod-phosphate.

Fingolimod-phosphate binds at low nanomolar concentrations to sphingosine-1-phosphate (S1P) receptors 1, 3, and 4 located on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptors 1, 3 and 5 located on neural cells in the central nervous system (CNS).

By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. Animal studies and *in vitro* experiments indicate that fingolimod may also exert beneficial effects in multiple sclerosis (MS) via interaction with S1P receptors on neural cells.

Heart rate and rhythm

Fingolimod causes an initial reduction in heart rate and atrio-ventricular conduction at treatment initiation (see section 4.8). The maximal decline of heart rate is seen in the first 6 hours post dose (Mean -7,86; SD 8,048; Min -43,7; Median -7,67; Max 24,0), with 70 % of the negative chronotropic effect achieved on the first day. Heart rate progressively returns to baseline values within one month of chronic treatment.

With initiation of fingolimod treatment there is an increase in atrial premature contractions, but there is no increased rate of atrial fibrillation/flutter or ventricular dysrhythmias or ectopy.

Fingolimod treatment is not associated with a decrease in cardiac output.

The decrease in heart rate induced by fingolimod can be reversed by atropine, isoprenaline or salmeterol.

Potential to prolong the QT interval

In a QT interval study of doses of 1,25 or 2,5 mg fingolimod at steady-state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a mean prolongation of QTcl, with the upper bound of the 90% CI ≤ 13,0 ms. There is no dose or exposure- response relationship of fingolimod and QTcl prolongation. There is no consistent signal of increased incidence of QTcl outliers, either absolute or change from baseline, associated with fingolimod treatment. In the multiple sclerosis studies, there was no clinically relevant prolongation of QT interval.

Pulmonary function

Fingolimod treatments with single or multiple doses of 0,5 and 1,25 mg for two weeks was not associated with a detectable increase in airway resistance as measured by FEV1 and forced expiratory flow during expiration of 25 to 75 % of the forced vital capacity (FEF_{25-75}).

Single fingolimod doses ≥ 5 mg (10-fold the recommended dose) are associated with a dose-dependent increase in airway resistance. Fingolimod treatment with multiple doses of 0,5; 1,25; or 5 mg was not associated with impaired oxygenation or oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Patients on fingolimod treatment had a normal bronchodilator response to inhaled beta-agonists.

5.2. Pharmacokinetic properties

Absorption

Fingolimod absorption is slow (t_{max} of 12 – 16 hours) and extensive (≥ 85 %, based on the amount of radioactivity excreted in urine and the amount of metabolites in faeces extrapolated to infinity). The apparent absolute oral bioavailability is high (93 %).
Food intake does not alter C_{max} or exposure (AUC) of fingolimod or fingolimod-phosphate.
Steady-state-blood concentrations are reached within 1 to 2 months following once-daily administration and steady-state levels are approximately 10-fold greater than with the initial dose.

Distribution

Fingolimod highly distributes in red blood cells, with the fraction in blood cells of 86 %. Fingolimod-phosphate has a smaller uptake in blood cells of < 17 %. Fingolimod and fingolimod-phosphate are highly protein bound (> 99,7 %). Fingolimod and fingolimod-phosphate protein binding is not altered by renal or hepatic impairment.
Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1 200 ± 260 litres.

Metabolism

The biotransformation of fingolimod in humans occurs by 3 main pathways: by reversible stereoselective phosphorylation to the pharmacologically active (S)-

enantiomer of fingolimod-phosphate, by oxidative biotransformation mainly via the cytochrome P450 4F2 isoenzyme, with subsequent fatty acid-like degradation to inactive metabolites, and by formation of pharmacologically inactive non-polar ceramide analogues of fingolimod.

Following single oral administration of [^{14}C] fingolimod, the major fingolimod-related components in blood, as judged from their contribution to the AUC up to 816 hours post-dose of total radiolabelled components, are fingolimod itself (23,3 %), fingolimod-phosphate (10,3 %), and inactive metabolites (M3 carboxylic acid metabolite (8,3 %), M29 ceramide metabolite (8,9 %), and M30 ceramide metabolite (7,3 %).

Elimination

Fingolimod blood clearance is 6,3 ± 2,3 litre/hour, and the average apparent terminal half-life ($t_{1/2}$) is 6 to 9 days. Blood levels of fingolimod-phosphate decline in parallel with those of fingolimod in the terminal phase, yielding similar half-lives for both.

After oral administration, about 81 % of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod-phosphate are not excreted intact in urine but are the major components in the faeces with amounts of each representing less than 2,5 % of the dose each. After 34 days, the recovery of the administered dose is 89 %.

Linearity

Fingolimod and fingolimod-phosphate concentrations increase in an apparent dose proportional manner after multiple once daily doses of fingolimod 0,5 mg or 1,25 mg.

Special Populations

Renal Impairment

In patients with severe renal impairment, fingolimod C_{max} and AUC are increased by 32 % and 43 %, respectively, and fingolimod-phosphate C_{max} and AUC are increased by 25 % and 14 %, respectively. The apparent elimination half-life is unchanged for both analytes.

Hepatic Insufficiency

In subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, and C), no change in fingolimod C_{max} was observed, but fingolimod AUC was increased respectively by 12 %, 44 %, and 103 %. In patients with severe hepatic impairment (Child-Pugh class C), fingolimod-phosphate C_{max} was decreased by 22 % and AUC was not substantially changed. The pharmacokinetics of fingolimod-phosphate were not evaluated in patients with mild or moderate hepatic impairment. The apparent elimination half-life of fingolimod is unchanged in subjects with mild hepatic impairment but is prolonged by about 50 % in patients with moderate or severe hepatic impairment. Fingolimod should not be used in patients with severe hepatic impairment (Child-Pugh class C) (see section 4.3).

Fingolimod should be introduced cautiously in mild and moderate hepatic impaired patients (see section 4.2).

Elderly

Clinical experience and pharmacokinetic information in patients aged above 65 years are limited. FINGOSOL 0.5 should be used with caution in patients aged 65 years and over.

Paediatric population

Safety and efficacy of fingolimod in paediatric patients under the age of 18 year have not been studied. Fingolimod is not indicated for use in paediatric patients.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Low-substituted hydroxypropyl cellulose

Magnesium stearate

Microcrystalline cellulose

Gelatine capsule shells

Iron oxide yellow

Titanium dioxide

Imprinting ink

Black iron oxide

Propylene glycol

Shellac

6.2. Incompatibilities

Not applicable

6.3. Shelf Life

36 months at or below 25 °C.

6.4. Special precautions for storage

Protect from moisture.

Keep blister strips in outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

For storage conditions, see section 6.3.

6.5. Nature and contents of container

FINGOSOL 0.5 is a hard gelatin capsule with a white opaque body and yellow opaque cap imprinted with “WF5” containing white to off-white powder

Silver aluminium/aluminium blister strips or silver aluminium/clear transparent PVDC/PVC blister strips containing 7, 10 or 14 capsules per blister strip.

Pack sizes:

7, 28, 30 or 98 capsules per carton.

(Not all pack sizes might be marketed)

6.6. Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

CIPLA MEDPRO (PTY) LTD

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Phone: +27 21 943 4200

Customer Care: 080 222 6662

E-mail: info@cipla.co.za

Drug Safety E-mail: drugsafety@cipla.co.za

8. MARKETING AUTHORISATION NUMBER(S)

To be allocated

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated

10. DATE OF REVISION OF THE TEXT

Not applicable.