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MODLIFIN 0,5 mg capsules should be used only by neurologists experienced in the treatment of multiple sclerosis. MODLIFIN induces a reduction in heart rate upon treatment initiation, which can lead to bradydysrhythmia. The effect is usually maximal on Day 1, within the first 6 hours and heart rate usually normalises by 1 month. However, these events may occur at any time. Hourly monitoring for at least 6 hours (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 (see section 4.4) 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.

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MODLIFIN 0,5 mg (Capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0,5 mg fingolimod (as hydrochloride).

MODLIFIN is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule.

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Bright yellow opaque/white opaque size “3” hard gelatin capsule imprinted with “FO 0,5 mg” on the cap and two radial bands on the capsule body with yellow ink containing white to off-white powder. Each capsule is approximately 15,8 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MODLIFIN is indicated as a disease modifying therapy for the treatment of patients with relapsing multiple sclerosis 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 **MODLIFIN** is one 0,5 mg capsule taken orally once daily, which can be taken with or without food. If a dose is missed treatment should be continued with the next dose as planned.

On initiation of **MODLIFIN** 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, bradydysrhythmia subsection).

For recommendations related to switching patients from other disease modifying therapies to **MODLIFIN**, see section 4.4: Prior treatment with immunosuppressive or immune-modulating therapies.

Special populations

Renal impairment

No **MODLIFIN** dose adjustments are needed in patients with renal impairment (see section 5.2).

Hepatic impairment

No **MODLIFIN** dose adjustments are needed in patients with mild or moderate hepatic impairment. **MODLIFIN** should be used with caution in patients with severe hepatic impairment (Child-Pugh class C) (see section 5.2).

Elderly

MODLIFIN should be used with caution in patients aged 65 years and over (see section 5.2).

Diabetic patients

MODLIFIN 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

MODLIFIN is not indicated for use in paediatric patients (see section 5.2).

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance, fingolimod, or to any of the excipients listed in section 6.1.
- Pregnancy and lactation.
- Concomitant administration with anti-dysrhythmic medicines; Class 1a (e.g., quinidine, procainamide), Class III (e.g., amiodarone, sotalol) (see section 4.4).
- Patients who in the last 6 months had myocardial infarction, unstable angina pectoris, stroke/ transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or New York Heart Association Class III/IV heart failure.

- Patients with severe cardiac dysrhythmias requiring anti-dysrhythmic treatment with Class Ia or Class III anti-dysrhythmic medicines (see section 4.4).
- Patients with second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not have a pacemaker (see section 4.4).
- Patients with a baseline QTc interval ≥ 500 msec (see section 4.4).
- Women of childbearing potential not using effective contraception.

4.4 Special warnings and precautions for use

Infections

Fingolimod, as in **MODLIFIN**, causes a dose dependent reduction of peripheral lymphocyte count to 20 to 30 % of baseline values.

This is due to the reversible sequestration of lymphocytes in lymphoid tissues (see section 5). The immune system effects (see section 5) of **MODLIFIN** may increase the risk of infections including opportunistic infections (see section 4.8).

Before initiating treatment with **MODLIFIN**, a recent complete blood count (CBC) (i.e. within 6 months or after discontinuation of prior therapy) should be available.

Initiation of treatment with MODLIFIN should be delayed in patients with severe active infection until resolution. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Because the elimination of MODLIFIN after discontinuation may take up to two months, vigilance for infection should be continued throughout this period (see below subsection: Stopping MODLIFIN therapy).

Progressive multifocal leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in the post-marketing setting (see section 4.8). PML is an opportunistic infection caused by JC virus, which may be fatal or result in severe disability. Cases of PML have occurred after approximately 2-3 years of treatment, although an exact relationship with the

duration of treatment is unknown. The incidence rate for PML appears to be higher for patients in Japan; the reasons are currently unknown. Additional PML cases have occurred in patients who had been treated previously with natalizumab, which has a known association with PML. Medical practitioners should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, **MODLIFIN** treatment should be suspended until PML has been excluded. MRI findings suggestive of PML may be apparent before clinical signs or symptoms. Cases of PML, diagnosed based on MRI findings and the detection of JVC DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, have been reported in patients treated with MS medications associated with PML, including **MODLIFIN**.

Cryptococcal meningitis

Cases of cryptococcal meningitis 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). Cryptococcal meningitis may be fatal. For this reason patients with symptoms and signs consistent with cryptococcal meningitis should undergo prompt diagnostic evaluation. If cryptococcal meningitis is diagnosed, appropriate treatment should be initiated and **MODLIFIN** should be discontinued until the patient has fully recovered.

Anti-neoplastic, immune-modulating or immunosuppressive therapies (including corticosteroids) should be co-administered with caution due to the risk of additive immunosuppressive effects (see section 4.5).

Specific decisions as to the dosage and duration of treatment with corticosteroids should be based on clinical judgment. Co-administration of a short course of corticosteroids (up to 5 days as per study protocols) did not increase the overall rate of infection in patients treated with fingolimod in the Phase III clinical trials, compared to placebo. Based on these data, short courses of corticosteroids (up to 5 days) can be used in combination with **MODLIFIN** (see sections 4.5 and 4.8).

Patients receiving **MODLIFIN** should be instructed to report symptoms of infections to their medical practitioner. Suspension of dosing with **MODLIFIN** should be considered if a patient develops a serious infection and consideration of benefit-risk should be undertaken prior to re-initiation of therapy.

Patients need to be assessed for their immunity to varicella (chickenpox) prior to **MODLIFIN** treatment. It is recommended that patients without a health care 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 **MODLIFIN** therapy. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with **MODLIFIN** (see section 4.8).
Initiation of treatment with **MODLIFIN** should be postponed for 1 month to allow full effect of vaccination to occur.

Human papilloma virus infection
Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported under treatment with fingolimod in the post-marketing setting. Due to the immunosuppressive properties of fingolimod, vaccination against HPV should be considered prior to treatment initiation with fingolimod taking into account vaccination recommendations. Cancer screening, including Pap test, is recommended as per standard of care.

Vaccination
Vaccination may be less effective during and for up to two months after stopping treatment with **MODLIFIN** (see below subsection: Stopping **MODLIFIN** therapy). The use of live attenuated vaccines should be avoided (see section 4.5).

Macular oedema
Macular oedema (see section 4.8) with or without visual symptoms has been reported in 0,5 % of patients treated with fingolimod 0,5 mg, as in **MODLIFIN**, occurring predominantly in the first 3 to 4 months of therapy. An

ophthalmic evaluation is therefore recommended at 3 to 4 months after treatment initiation. If patients report visual disturbances at any time while on **MODLIFIN** therapy, 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). Fingolimod 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 ophthalmic evaluation prior to initiating **MODLIFIN** therapy and have follow-up evaluations while receiving **MODLIFIN** therapy. Continuation of fingolimod in patients with macular oedema has not been evaluated. A decision on whether or not **MODLIFIN** therapy should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Bradydysrhythmia

Initiation of **MODLIFIN** treatment results in a decrease in heart rate. After the first dose, the heart rate decrease starts within an hour and the Day 1 decline is usually maximal within 6 hours and usually normalises by one month (see sections 4.3 and 4.4).

With continued dosing, heart rate usually returns to baseline within one month of chronic treatment (see Heart rate and rhythm subsection in section 5). In patients receiving fingolimod 0,5 mg this decrease in heart rate, as measured by pulse, averages approximately 8 beats per minute (bpm). Heart rates below 40 bpm have been observed (see section 4.8). Patients who experienced bradycardia were generally asymptomatic but some patients experienced mild to moderate symptoms, including hypotension, dizziness, fatigue and/or palpitations, which usually resolved within the first 24 hours of treatment.

Initiation of fingolimod treatment is associated with atrioventricular conduction delays, usually first-degree atrioventricular blocks (prolonged PR interval on electrocardiogram). Second-degree atrioventricular blocks, usually Mobitz type I (Wenckebach) have been observed in less than 0,2 % of patients receiving fingolimod 0,5

mg. The conduction abnormalities typically were transient, asymptomatic, usually did not require treatment and usually resolved within the first 24-hours on treatment (see section 4.8).

Cases of transient, complete AV block have been reported during post-marketing use of fingolimod (see section 4.8).

Therefore on initiation of **MODLIFIN** treatment, it is recommended that all patients be observed, with hourly pulse and blood pressure measurement, for a period of 6 hours for signs and symptoms of bradycardia. All patients should have an electrocardiogram performed prior to dosing and at the end of the 6-hour monitoring period.

Should post-dose bradydysrhythmia-related symptoms occur, appropriate management should be initiated as necessary and the patient should be observed until the symptoms have resolved.

Should a patient require pharmacological intervention during the first dose observation period, overnight monitoring in a medical facility should be instituted and the first dose monitoring strategy should be repeated after the second dose of **MODLIFIN**.

Additional observation until the finding has resolved is also required:

- if the heart rate at 6 hours post-dose is <45 bpm or is the lowest value post-dose (suggesting that the maximum pharmacodynamic effect on the heart is not yet manifest)
- or if the ECG at 6 hours after the first dose shows new onset second degree or higher AV block

If the ECG at 6 hours after the first dose shows a QTc interval ≥500 msec, patients should be monitored overnight.

Due to the risk of serious cardiac rhythm disturbances, **MODLIFIN** should not be used in patients with a history of symptomatic bradycardia, recurrent syncope or sino-atrial heart block. Since initiation of **MODLIFIN** treatment results in decreased heart rate and therefore a prolongation of the QT interval, **MODLIFIN** should not be used in patients with significant QT prolongation (QTc >470 msec [adult females], QTc >460 msec [paediatric females] or >450 msec [adult and paediatric males]) (see section section 4.3). **MODLIFIN** is best avoided in patients with relevant risk factors for QT prolongation, for example, hypokalemia, hypomagnesemia or congenital QT

prolongation. Since significant bradycardia may be poorly tolerated in patients with a history of cardiac arrest, uncontrolled hypertension, history of recurrent syncope, or severe untreated sleep apnoea, **MODLIFIN** should not be used in these patients. If treatment is considered in patients for whom **MODLIFIN** is not contraindicated, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy, which should last overnight.

Fingolimod has not been studied in patients with dysrhythmias requiring treatment with Class Ia (e.g. quinidine, procainamide) or Class III anti-dysrhythmic medicines (e.g., amiodarone, sotalol). Class Ia and Class III anti-dysrhythmic medicines have been associated with cases of Torsades de Pointes in patients with bradycardia.
Since initiation of **MODLIFIN** treatment results in decreased heart rate, **MODLIFIN** should not be co-administered with these medicines.

Experience with fingolimod is limited in patients receiving concurrent therapy with beta blockers, heart rate lowering calcium channel blockers (such as verapamil or diltiazem), or other substances that may decrease heart rate (e.g. ivabradine or digoxin). Since the initiation of fingolimod treatment is also associated with slowing of the heart rate, concomitant use of these substances during **MODLIFIN** initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with **MODLIFIN** should not be used in patients who are concurrently treated with these substances. If treatment with **MODLIFIN** is considered, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicines or appropriate monitoring for treatment initiation, which should last overnight (see section 4.5).
If **MODLIFIN** therapy is discontinued for more than 2 weeks after the first month of treatment the effects on heart rate and atrioventricular conduction may recur on reintroduction of **MODLIFIN** treatment and the same precautions as for the first dose should apply. Within the first two weeks of treatment, first dose procedures are recommended after an interruption of one day or more. During weeks 3 and 4 of treatment first dose procedures are recommended after treatment interruption of more than seven days.

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Liver function

Increased hepatic enzymes, mostly alanine aminotransaminase (ALT) elevation, have been reported in multiple sclerosis patients treated with fingolimod. In clinical trials, a 3-fold or greater elevation in ALT occurred in 8,0 % of patients treated with fingolimod 0,5 mg and the medicine was discontinued if the elevation exceeded a 5-fold increase. Recurrence of ALT elevations occurred upon re-challenge in some patients, supporting a relationship to the medicine. Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with **MODLIFIN**. Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine during treatment, should have liver enzymes checked and **MODLIFIN** should be discontinued if significant liver injury is confirmed (see section 4.8).

Although it is not known whether patients with preexisting liver disease are at increased risk to develop elevated liver function test (LFT) values when taking **MODLIFIN**, caution should be exercised when using **MODLIFIN** in patients with a history of liver disease.

Posterior reversible encephalopathy syndrome

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported at 0,5 mg dose in clinical trials and in the post-marketing setting (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, **MODLIFIN** should be discontinued.

Prior treatment with immunosuppressive or immune-modulating therapies

When switching from other disease modifying therapies, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimising risk of disease reactivation. Before initiating treatment with **MODLIFIN**, a recent complete blood cell count (i.e. after

discontinuation of prior therapy) should be available to ensure any immune effects of such therapies (e.g. cytopenia) have resolved.

Beta interferon, glatiramer acetate or dimethyl fumarate

MODLIFIN can generally be started immediately after discontinuation of beta interferon, glatiramer acetate or dimethyl fumarate.

Natalizumab or teriflunomide

Due to the long half-life of natalizumab or teriflunomide, caution regarding potential additive immune effects is required when switching patients from these therapies to **MODLIFIN**. A careful case-by-case assessment regarding the timing of the initiation of Modifin treatment is recommended.

Elimination of natalizumab 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 several months to up to 2-years. An accelerated elimination procedure is described in the teriflunomide product information.

Accelerated elimination procedure: Cholestyramine and activated charcoal

The elimination of teriflunomide from the circulation can be accelerated by administration of cholestyramine or activated charcoal, presumably by interrupting the reabsorption processes at the intestinal level.

Teriflunomide concentrations measured during an 11-day procedure to accelerate teriflunomide elimination with either 8 g cholestyramine three times a day, 4 g cholestyramine three times a day or 50 g activated charcoal twice a day following cessation of teriflunomide treatment have shown that these regimens were effective in accelerating teriflunomide elimination, leading to more than 98 % decrease in teriflunomide plasma concentrations, with cholestyramine being faster than charcoal. Following discontinuation of teriflunomide and the administration of cholestyramine 8 g three times a day, the plasma concentration of teriflunomide is reduced 52 % at the end of day 1, 91 % at the end of day 3, 99,2 % at the end of day 7, and 99,9 % at the completion of day 11. The choice

between the 3 elimination procedures should depend on the patient's tolerability. If cholestyramine 8 g three times a day is not well tolerated, cholestyramine 4 g three times a day can be used. Alternatively, activated charcoal may also be used (the 11 days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly).

Alemtuzumab

Due to the characteristics and duration of alemtuzumab immune suppressive effects described in its product information, initiating treatment with **MODLIFIN** after alemtuzumab is not recommended.

Respiratory effects

Minor dose-dependent reductions in values for forced expiratory volume (FEV_1) and diffusion capacity for carbon monoxide (DLCO) were observed with fingolimod treatment starting at month 1 and remaining stable thereafter. **MODLIFIN** should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive

pulmonary disease (see section 4.8).

Return of disease activity (rebound) after **MODLIFIN** discontinuation

Cases of severe exacerbation of disease have been reported after stopping fingolimod in the post-marketing setting. This was generally observed within 12 weeks after stopping fingolimod, but was also reported up to and beyond 24 weeks after fingolimod discontinuation. Therefore, caution is indicated when stopping fingolimod therapy.

If discontinuation of fingolimod is deemed necessary, patients should be monitored for relevant signs and symptoms and appropriate treatment should be initiated as required.

Cutaneous Malignancies

Basal cell carcinoma (BCC) and other cutaneous neoplasms including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma, have been reported in patients receiving fingolimod (see section 4.8). Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Since there is, a potential risk of malignant skin growths, patients treated with fingolimod should be cautioned against exposure to sunlight without protection.

Lymphomas

There have been cases of lymphoma in clinical studies and the post-marketing setting. The cases reported were heterogeneous in nature, mainly Non-Hodgkin's Lymphoma, including B- cell and T-cell lymphomas. Cases of cutaneous T-cell lymphoma (mycosis fungoides) have been observed (see section 4.8).

Tumefactive lesions

Rare cases of tumefactive lesions associated with MS relapse were reported in the post-marketing setting. In case of severe relapses, MRI should be performed to exclude tumefactive lesions. Discontinuation of treatment should be considered by the medical practitioner on a case-by-case basis taking into account individual benefits and risks.

Stopping therapy

If a decision is made to stop treatment with **MODLIFIN**, the medical practitioner needs to be aware that fingolimod remains in the blood and has pharmacodynamic effects, such as decreased lymphocyte counts, for up to two months following the last dose. Lymphocyte counts typically return to normal range within 1-2 months of stopping therapy (see section 5). Starting other therapies during this interval will result in a concomitant exposure to fingolimod. Use of immunosuppressants soon after the discontinuation of **MODLIFIN** may lead to an additive effect on the immune system and therefore caution should be applied.

Interference with serological testing

Since fingolimod 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 **MODLIFIN**. Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the

number of circulating lymphocytes.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Anti-neoplastic, immunomodulatory or immunosuppressive therapies

Other anti-neoplastic, immunosuppressive or immune modulating therapies should be co-administered with caution due to the risk of additive immune system effects. Specific decisions as to the dosage and duration of concomitant treatment with corticosteroids should be based on clinical judgment (see sections 4.4 and 4.8).

Caution should also be applied when switching patients from other long-acting therapies with immune effects such as natalizumab, teriflunomide or mitoxantrone (see section 4.4).

Bradycardia-inducing medicines

When MODLIFIN is used with beta blockers, there is an additional 15 % reduction in heart rate upon MODLIFIN initiation, an effect not seen with calcium channel blockers. Treatment with MODLIFIN should not be initiated in patients receiving beta blockers, heart rate lowering calcium channel blockers (such as verapamil or diltiazem), or other substances which may decrease heart rate (e.g. ivabradine or digoxin) because of the potential additive effects on heart rate. If treatment with MODLIFIN is considered, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicines or appropriate monitoring for treatment initiation, which should last overnight (see section 4.4).

Vaccination

During and for at least two months after treatment with **MODLIFIN** vaccination may be less effective. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided (see sections 4.4 and 4.8).

Pharmacokinetic interactions

Fingolimod is primarily cleared via cytochrome P450 4F2 (CYP4F2) and possibly other CYP4F isoenzymes. *In vitro* studies in hepatocytes indicated that CYP3A4 may contribute to fingolimod metabolism in the case of strong induction of CYP3A4.

Potential of **MODLIFIN** and fingolimod-phosphate to inhibit the metabolism of co-medications

In vitro inhibition studies using pooled human liver microsomes and specific metabolic probe substrates demonstrated that fingolimod and fingolimod-phosphate have little or no capacity to inhibit the activity of CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9 CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 or CYP4A9/11 (fingolimod only)). Therefore, **MODLIFIN** and fingolimod-phosphate are unlikely to reduce the clearance of medicines that are mainly cleared through metabolism by the major cytochrome P isoenzymes.

Potential of **MODLIFIN** and fingolimod-phosphate to induce its own and/or the metabolism of co-medications

Fingolimod was examined for its potential to induce human CYP3A4, CYP1A2, CYP4F2 and ABCB1 (P-gp) mRNA and CYP3A, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP4F2 activity in primary human hepatocytes. Fingolimod did not induce mRNA or activity of the different CYP enzymes and ABCB1 with respect to the vehicle control. Therefore no clinically relevant induction of the tested CYP enzymes or ABCB1 (P-gp) by **MODLIFIN** are expected at therapeutic concentrations.

In vitro experiments did not provide an indication of CYP induction by fingolimod-phosphate.

Potential of **MODLIFIN** and fingolimod-phosphate to inhibit the active transport of co-medications

Based on *in vitro* data, fingolimod as well as fingolimod-phosphate are not expected to inhibit the uptake of co-medications and/or biologics transported by the organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1, OATP1B3) or the sodium taurocholate co-transporting polypeptide (NTCP). Similarly, they are not expected to inhibit the efflux of co-medications and/or biologics transported by the breast cancer resistance protein (BCRP), the bile salt export pump (BSEP), the multi-medicine resistance-associated protein 2 (MRP2) or P-glycoprotein (P-gp) at therapeutic concentrations.

Oral contraceptives

The co-administration of fingolimod with oral contraceptives (ethinylestradiol 30 micrograms and levonorgestrel 150 micrograms) did not elicit any change in oral contraceptive exposure. Fingolimod and fingolimod-phosphate exposure were consistent with those from previous studies. No interaction studies have been performed with oral contraceptives containing other progestogens. No studies with implanted or injected contraceptives have been performed.

Ciclosporin

The pharmacokinetics of single-dose fingolimod were not altered during co-administration with ciclosporin at steady-state, nor were ciclosporin steady-state pharmacokinetics altered by single-dose or multi-dose (28 days) fingolimod administration. These data indicate that **MODLIFIN** is unlikely to reduce or increase the clearance of medicines mainly cleared by CYP3A4 and that inhibition of CYP3A4 is unlikely to reduce the clearance of **MODLIFIN**. Potent inhibition of transporters P-gp, MRP2 and OATP1B1 does not influence **MODLIFIN** disposition.

Ketoconazole

The co-administration of ketoconazole 200 mg twice daily at steady-state and a single dose of fingolimod 5 mg led to a modest increase in the AUC of fingolimod and fingolimod-phosphate (1,7-fold increase) by inhibition of CYP4F2.

Isoproterenol, atropine, atenolol and diltiazem

Single-dose fingolimod and fingolimod-phosphate exposure was not altered by co-administered isoproterenol, or atropine. Likewise, the single-dose pharmacokinetics of fingolimod and fingolimod-phosphate and the steady-state pharmacokinetics of both atenolol and diltiazem were unchanged during the co-administration of the latter two medicines with fingolimod.

Carbamazepine

The 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 fingolimod-phosphate, by approximately 40 %. The clinical relevance of this decrease is unknown.

Population pharmacokinetics analysis of potential medicine-medicine interactions

A population pharmacokinetics evaluation, performed in multiple sclerosis patients, did not provide evidence for a significant effect of fluoxetine and paroxetine (strong CYP2D6 inhibitors) on fingolimod or fingolimod-phosphate concentrations. In addition, the following, commonly prescribed substances had no clinically relevant effect (≤ 20 %) on fingolimod or fingolimod-phosphate concentrations: baclofen, gabapentin, oxybutynin, amantadine, modafinil, amitriptyline, pregabalin, corticosteroids and oral contraceptives.

Laboratory tests

Since fingolimod 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 fingolimod.

Laboratory tests requiring the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes.

4.6 Fertility, pregnancy and lactation

MODLIFIN should not be used in pregnancy and lactation (see section 4.3).

Safety in pregnancy and lactation has not been established. Fingolimod is teratogenic in animals.

Women of childbearing potential

Due to risk to the foetus, fingolimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for 2 months after treatment discontinuation.

Pregnancy

Based on human experience, post-marketing data suggest that the use of fingolimod is associated with a 2-fold increased risk of major congenital malformation when administered during pregnancy compared with the general population. The following major malformations were most frequently reported:

- Congenital heart disease such as atrial and ventricular septal defects, tetralogy of Fallot
- Renal abnormalities
- Musculoskeletal abnormalities

If **MODLIFIN** is discontinued because of pregnancy or planned pregnancy, the possible return of disease activity should be considered (see section 4.4 - Return of disease activity (rebound) after **MODLIFIN** discontinuation and stopping therapy).

Breastfeeding

MODLIFIN is contraindicated in breastfeeding (see section 4.3). Fingolimod is excreted in the milk of treated animals during lactation. Due to the potential for serious adverse reactions to fingolimod in nursing infants, women receiving **MODLIFIN** should not breastfeed.

Fertility

Fingolimod is present in seminal ejaculate.

Safety regarding an increased risk of male mediated foetal toxicity has not been demonstrated. Data from preclinical studies do not suggest that fingolimod would be associated with an increased risk of reduced fertility.

4.7 Effects on ability to drive and use machines

The clinical status of the patient and adverse event profile of **MODLIFIN** should be borne in mind when considering the patients ability to perform tasks that require judgement, motor and cognitive skills. Driving may be impaired by such adverse events.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions were headache, increased hepatic enzyme, diarrhoea, cough, influenza, sinusitis and back pain.

Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Infections and infestations	Frequent	Influenza, sinusitis, herpes viral infections, bronchitis, tinea versicolor
	Less frequent	Pneumonia
	Frequency unknown	Progressive multifocal leukoencephalopathy (PML)* Cryptococcal infections*
	Frequent	Basal cell carcinoma

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Neoplasms, benign, malignant and unspecified (including cysts and polyps)	Less frequent	Malignant melanoma, lymphoma**, squamous cell carcinoma, Kaposi's sarcoma**
	Frequency unknown	Merkel cell carcinoma**
Blood and lymphatic system disorders	Frequent	Lymphopenia, leucopenia
	Less frequent	Thrombocytopenia
	Frequency unknown	Autoimmune haemolytic anaemia** 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, migraine
	Less frequent	Seizure, Posterior reversible encephalopathy syndrome (PRES)
	Frequency unknown	Severe exacerbation of disease after fingolimod discontinuation**
Eye disorders	Frequent	Vision blurred
	Less frequent	Macular oedema

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Cardiac disorders	Frequent	Bradycardia, atrioventricular 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**
Hepato-biliary disorders	Frequency unknown	Acute hepatic failure**
Skin and subcutaneous tissue disorders	Frequent	Eczema, alopecia, pruritus
Musculoskeletal, connective tissue and bone disorders	Frequent	Back pain, myalgia, arthralgia
General disorders and administration site conditions	Frequent	Asthenia
Investigations	Frequent	Hepatic enzyme increased (increased alanine transaminase, gamma glutamyl transferase, aspartate transaminase) Weight decreased** Blood triglycerides increased
	Less frequent	Neutrophil count decreased

*PML and cryptococcal infections have been reported post-marketing.

**Adverse reactions from spontaneous reports and literature.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

MODLIFIN 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 **MODLIFIN** it is important to observe 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 sections 4.2 and 4.4).

Neither dialysis nor plasma exchange would result in meaningful removal of **MODLIFIN** from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 34 Other: selective immunosuppressive agents

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA27

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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.

By acting as a functional antagonist of S1PR on lymphocytes, fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes.

This redistribution reduces the infiltration of lymphocytes, including pro-inflammatory Th17 cells, into the central nervous system where they would be involved in nerve inflammation and nervous tissue damage.

Animal studies and in vitro experiments indicate that fingolimod may also exert beneficial effects in multiple sclerosis via interaction with S1P receptors on neural cells. Fingolimod penetrates the CNS, and has been shown in animals, to reduce astrogliosis, demyelination and neuronal loss. Further, fingolimod treatment increases the levels of brain derived neurotropic factor (BDNF) in the cortex, hippocampus and striatum of the brain of mice to support neuronal survival and improve motor functions.

<u>Immune system</u>

Effects on immune cell numbers in the blood. Within 4 to 6 hours after the first dose of fingolimod 0,5 mg, the lymphocyte count decreases to approximately 75 % of baseline. With continued daily dosing, the lymphocyte count continues to decrease over a two-week period, reaching a nadir count of approximately 500 cells/µl or approximately 30 % of baseline. Eighteen percent of patients reached a nadir of < 200 cells/µl on at least one

occasion. Low lymphocyte counts are maintained with chronic daily dosing. Peripheral lymphocyte count increases are evident within days of stopping fingolimod treatment and typically normal counts are reached within one to two months. Chronic fingolimod dosing leads to a decrease in the neutrophil count to approximately 80 % of baseline. Monocytes are unaffected by fingolimod.

Heart rate and rhythm

Fingolimod causes an initial reduction in heart rate and atrioventricular 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 QTcI, with the upper boundary of the 90 % CI ≤ 13,0 msec. 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. In the multiple sclerosis studies, there was no clinically relevant prolongation of the QT interval.

Pulmonary function

Fingolimod treatment with single or multiple doses of 0,5 and 1,25 mg for two weeks is 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 (FEF25-75). However, 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 is not associated with impaired oxygenation or oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Subjects on fingolimod treatment have a normal bronchodilator response to inhaled β-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 of 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 L.

Fingolimod readily distributes into the brain and low levels are detected in seminal ejaculate.

Biotransformation

The biotransformation of fingolimod in humans occurs by three main pathways; by reversible stereoselective phosphorylation to the pharmacologically active (*S*)-enantiomer of fingolimod-phosphate, by oxidative

biotransformation catalysed mainly by CYP4F2 and possibly other CYP4F isoenzymes and subsequent fatty acid-like degradation to inactive metabolites, and by formation of pharmacologically inactive non-polar ceramide analogs 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 l/h, and the average apparent terminal half-life ($t_{1/2}$) is 6 to 9 days.

Blood levels of fingolimod-phosphate decline in parallel with fingolimod in the terminal phase yielding similar half-lives for both.

After an 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 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

Severe renal impairment increases fingolimod C_{max} and AUC by 32 % and 43 %, respectively, and fingolimod-phosphate C_{max} and AUC by 25 % and 14 %, respectively. The apparent elimination half-life is unchanged for both analytes.

Hepatic Impairment

The pharmacokinetics of single-dose fingolimod (1 or 5 mg), when assessed in subjects with mild, moderate and severe hepatic impairments, (Child-Pugh class A, B, and C), showed no change on fingolimod C_{max}, but an increase in AUC by 12 %, 44 % and 103 %, respectively. The apparent elimination half-life is unchanged in mild hepatic impairment but is prolonged by 49 to 50 % in moderate and severe hepatic impairment.

In patients with severe hepatic impairment (Child-Pugh class C), fingolimod-phosphate C_{max} was decreased by 22 % and AUC increased by 38 %. The pharmacokinetics of fingolimod-phosphate were not evaluated in patients with mild or moderate hepatic impairment.

Although hepatic impairment elicited changes in the disposition of fingolimod and fingolimod-phosphate, the magnitude of these changes suggests that the fingolimod dose does not need to be adjusted in mild or moderate hepatic impaired patients (Child-Pugh class A and B). Fingolimod should be used with caution in patients with severe hepatic impairment (Child-Pugh class C).

Elderly

The mechanism for elimination and results from population pharmacokinetics suggest that dose adjustment would not be necessary in elderly patients. However, clinical experience in patients aged above 65 years is limited.

Paediatrics

Safety and efficacy of **MODLIFIN** in paediatric patients below the age of 18 have not been studied. **MODLIFIN** is not indicated for use in paediatric patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch, pregelatinised

Magnesium stearate

Capsule composition

CAP

Gelatin

Water

Titanium dioxide (E171)

Iron oxide yellow (E172)

BODY

Gelatin

Water

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

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MODLIFIN 0,5 mg capsules are packed in Alu-PVC/PVdC blister packs comprising lidding foil made of plain aluminium foil and clear PVC/PVdC film as forming foil.

Pack sizes: 10 & 30

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Building 2, Tuscany Office Park,

6 Coombe Place

Rivonia

Johannesburg

South Africa

8. REGISTRATION NUMBER(S)

56/34/0213

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 April 2023

10. DATE OF REVISION OF THE TEXT

18 April 2023