NOVARTIS

TUVIGIN®

0,5 mg fingolimod (as hydrochloride)

capsule

Professional Information

Document status: Final

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PROFESSIONAL INFORMATION

TUVIGIN should be used only by neurologists experienced in the treatment of multiple sclerosis. TUVIGIN 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 5.2*) 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

TUVIGIN 0,5 mg (capsules)

2 QUALITIVE AND QUANTITIVE COMPOSITION

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

TUVIGIN contains sugar (mannitol)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

TUVIGIN 0,5 mg capsules: Capsule with white opaque body and bright yellow cap; radial imprint with black ink, “FTY 0.5 mg” on the cap and two radial bands imprinted on the capsule body with yellow ink, containing white to almost white powder. Capsule size: 3.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TUVIGIN 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

Do not exceed the recommended dosage

The recommended dose of TUVIGIN 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 TUVIGIN 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*).

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

Special populations

Elderly population

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

Renal impairment

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

Hepatic impairment

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

Diabetic patients

TUVIGIN 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

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

Method of administration

TUVIGIN is for oral use.

4.3 Contraindications

- Hypersensitivity to fingolimod or any of the ingredients of TUVIGIN.
- Pregnancy and lactation.
- Concomitant administration with anti-dysrhythmic medicines; Class Ia (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 arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs (*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 (*see sections 4.4 and 4.6)*.

4.4 Special warnings and precautions for use

Infections

TUVIGIN 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 TUVIGIN may increase the risk of infections including opportunistic infections (*see section 4.8*).

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

Initiation of treatment with TUVIGIN 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 TUVIGIN after discontinuation may take up to two months, vigilance for infection should be continued throughout this period (see below subsection: *Stopping TUVIGIN therapy*).

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 the estimated risk appears to increase with cumulative exposure over time, an exact relationship with the duration of treatment is

unknown. The incidence rate of 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. During routine MRI (in accordance with national and local recommendations), medical practitioners should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, TUVIGIN 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 TUVIGIN.

Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with sphingosine 1-phosphate (S1P) receptor modulators, including fingolimod, who developed PML and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. The time to onset of IRIS in patients with PML was usually from weeks to months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.

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 TUVIGIN 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 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 TUVIGIN (see *section 4.5* and *4.8)*.

Patients receiving TUVIGIN should be instructed to report symptoms of infections to their medical practitioner. Suspension of dosing with TUVIGIN 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 TUVIGIN 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 TUVIGIN therapy. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with TUVIGIN (see *section 4.8*). Initiation of treatment with TUVIGIN should be postponed for 1 month to allow full effect of vaccination to occur.

Human Papilloma Virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported under treatment with TUVIGIN in the post-marketing setting (see *section 4.8*). Due to the immunosuppressive properties of fingolimod, vaccination against HPV should be considered prior to treatment initiation with TUVIGIN taking into account vaccination recommendations. Cancer screening, including Pap test, is recommended as per standard of care.

Vaccination may be less effective during and or up to two months after stopping treatment

with TUVIGIN (see below subsection: Stopping TUVIGIN 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 TUVIGIN 0,5 mg, 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 TUVIGIN 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*). TUVIGIN has not been studied in multiple sclerosis patients with concomitant diabetes mellitus. It is recommended that multiple sclerosis patients with diabetes or a history of uveitis undergo an ophthalmic evaluation prior to initiating TUVIGIN therapy and have follow-up evaluations while receiving TUVIGIN therapy.

Continuation of TUVIGIN in patients with macular oedema has not been evaluated. A decision on whether or not TUVIGIN therapy should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Bradydysrhythmia

Initiation of TUVIGIN 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 *section 4.3 and 4.4*).

With continued dosing, heart rate usually returns to baseline within one month of chronic treatment (see *section 5:1: Heart rate and rhythm*). In patients receiving TUVIGIN 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 TUVIGIN 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 TUVIGIN 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 TUVIGIN (see *section 4.8*).

Therefore, on initiation of TUVIGIN 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 TUVIGIN.
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, TUVIGIN should not be used in patients with a history of symptomatic bradycardia, recurrent syncope or sino-atrial heart block. Since initiation of TUVIGIN treatment results in decreased heart rate and therefore a prolongation of the QT interval, TUVIGIN 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 4.3*). TUVIGIN is best avoided in patients with relevant risk factors for QT prolongation, for example, hypokalaemia, 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, TUVIGIN should not be used in these patients. If treatment is considered in patients for whom TUVIGIN 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.

TUVIGIN 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 TUVIGIN treatment results in decreased heart rate, TUVIGIN should not be co-administered with these medicines.

Experience with TUVIGIN 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 TUVIGIN treatment is also associated with slowing of the heart rate (see “Brady dysrhythmia”), concomitant use of these substances during TUVIGIN initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with TUVIGIN should not be used in patients who are concurrently treated with these

substances. If treatment with TUVIGIN 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 TUVIGIN 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 TUVIGIN 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.

Liver function

Increased hepatic enzymes, mostly alanine amino transaminase (ALT) elevation, have been reported in multiple sclerosis patients treated with TUVIGIN. In clinical trials, a 3-fold or greater elevation in ALT occurred in 8,0 % of patients treated with TUVIGIN 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.

Clinically significant liver injury has occurred in patients treated with TUVIGIN in the post-marketing setting (see section 4.8). Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, have occurred as early as ten days after the first dose and have also been reported after prolonged use. Cases of acute liver failure requiring liver transplant have been reported.

Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with TUVIGIN and should be monitored periodically while on treatment and until two months after TUVIGIN discontinuation.

Patients should be monitored for signs and symptoms of hepatic injury. Liver transaminase and bilirubin levels should be measured promptly in patients who report symptoms that may indicate liver injury, such as unexplained nausea, vomiting, abdominal pain, right upper abdominal discomfort, new or worsening fatigue, anorexia, or jaundice and/or dark urine.

In this clinical context, if the patient is found to have an alanine aminotransferase (ALT) greater than three times the reference range and serum total bilirubin greater than two times the reference range, treatment with TUVIGIN should be interrupted. Treatment should not be resumed unless a plausible alternative etiology for the signs and symptoms of liver injury can be established.

Although it is not known whether patients with pre-existing liver disease are at increased risk to develop elevated liver function test (LFT) values when taking TUVIGIN, caution should be exercised when using TUVIGIN 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, TUVIGIN should be discontinued.

Prior treatment with immunosuppressive or immune-modulating therapies

When switching from other disease modifying therapies, the elimination 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 TUVIGIN, 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

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

Natalizumab or teriflunomide

Due to the long elimination half-life of natalizumab or teriflunomide, caution regarding potential additive immune effects is required when switching patients from these therapies to TUVIGIN. A careful case-by-case assessment regarding the timing of the initiation of TUVIGIN 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 TUVIGIN after alemtuzumab is not recommended.

Return of disease activity (rebound) after TUVIGIN discontinuation

Cases of severe exacerbation of disease have been reported after stopping TUVIGIN in the post-marketing setting. This was generally observed within 12 weeks after stopping TUVIGIN, but was also reported up to and beyond 24 weeks after TUVIGIN discontinuation. Therefore, caution is indicated when stopping TUVIGIN therapy. If discontinuation of TUVIGIN is deemed necessary, patients should be monitored for relevant signs and symptoms and appropriate treatment should be initiated as required.

Malignancies

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 TUVIGIN (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 TUVIGIN 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 TUVIGIN 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 TUVIGIN, 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 TUVIGIN. Use of immunosuppressants soon after the discontinuation of TUVIGIN may lead to an additive effect on the immune system and therefore caution should be applied. *(See* above subsection: *Return of disease activity (rebound) after TUVIGIN discontinuation)*

After stopping fingolimod in the setting of PML, it is recommended to monitor patients for development of immune reconstitution inflammatory syndrome (PML-IRIS) (see “Progressive multifocal leukoencephalopathy” above).

Mannitol Warning:

TUVIGIN contains mannitol and may have a laxative effect.

Patients with the rare hereditary condition of mannitol intolerance should not take TUVIGIN.

4.5 Interaction with other medicines and other forms of Interaction

Pharmacodynamic interactions

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 *section 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: Prior treatment with immunosuppressive or immune-modulating therapies*).

When TUVIGIN is used with beta-blockers, there is an additional 15 % reduction in heart rate upon TUVIGIN initiation, an effect not seen with calcium channel blockers. Treatment with TUVIGIN 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 TUVIGIN is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering medicinal products or appropriate monitoring for treatment initiation, which should last overnight (see *section 4.4*).

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

Pharmacokinetic interactions

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

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

TUVIGIN 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 TUVIGIN are expected at therapeutic concentrations.

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

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

Based on *in vitro* data, TUVIGIN 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 TUVIGIN with oral contraceptives (ethinylestradiol 30 micrograms and levonorgestrel 150 micrograms) did not elicit any change in oral contraceptive exposure. TUVIGIN 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 TUVIGIN 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) TUVIGIN administration. These data indicate that TUVIGIN 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 TUVIGIN. Potent inhibition of transporters P-gp, MRP2 and OATP1B1 does not influence TUVIGIN disposition.

Ketoconazole

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

Isoproterenol, atropine, atenolol and diltiazem

Single-dose TUVIGIN and fingolimod-phosphate exposure was not altered by co-administered isoproterenol, or atropine. Likewise, the single-dose pharmacokinetics of TUVIGIN 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 TUVIGIN.

Carbamazepine

The co-administration of carbamazepine 600 mg twice daily at steady-state and a single dose of TUVIGIN 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 TUVIGIN or fingolimod-phosphate concentrations: baclofen, gabapentin, oxybutynin, amantadine, modafinil, amitriptyline, pregabalin, corticosteroids and oral contraceptives.

Laboratory tests

Since TUVIGIN 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 TUVIGIN.

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

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

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

Women of childbearing potential / Contraception in males and females

TUVIGIN is contraindicated in women of childbearing potential not using effective contraception (see *section 4.3*). Therefore, before initiation of TUVIGIN treatment in women

of childbearing potential, a negative pregnancy result must be available and counselling should be regarding the serious risk to the foetus. Women of childbearing potential must use effective contraception during treatment and for 2 months after discontinuation of TUVIGIN since fingolimod takes approximately 2 months to eliminate from the body after treatment discontinuation (see *section 4.4*).

When stopping TUVIGIN treatnent for planning a pregnancy the possible return of disease activity should be considered (see *section 4.4: Return of disease activity (rebound) after TUVIGIN discontinuation and stopping therapy*).

Male reproductive toxicity

Fingolimod is present in seminal ejaculate.

Safety regarding an increased risk of male mediated foetal toxicity has not been demonstrated.

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.

Breastfeeding

TUVIGIN 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 TUVIGIN should not breatfeed.

Fertility

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 TUVIGIN 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

a. Summary of the safety profile

The safety population of TUVIGIN represents a total of 783 patients on TUVIGIN 0,5 mg.

In the pooled data from studies, the most serious adverse reactions (ADRs) for the 0,5 mg recommended therapeutic dose were infections, macular oedema and transient atrio-ventricular blocks on treatment initiation.

The most frequent ADRs (incidence ≥ 10 %) at the 0,5 mg dose were headache, influenza, diarrhoea, sinusitis, back pain, hepatic enzyme increased and cough. The most frequent adverse event reported for TUVIGIN 0,5 mg at an incidence greater than 1 % leading to treatment interruption was ALT elevations (2,2 %).

b. Tabulated list of adverse reactions

The table below presents the frequency of ADRs reported in the pooled analysis of placebo-controlled studies.

ADRs are listed according to MedDRA system organ class. Frequencies were defined according to the CIOMS classification as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000, <1/1000); very rare (<1/10 000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Tabulated summary of adverse drug reactions

Primary system organ class **Preferred Term**	**Fingolimod 0,5 mg N=783 (%)**	**Frequency range for the 0,5 mg dose**
Infections and infestations		
Influenza	89 (11,4)	very common
Sinusitis	85 (10,9)	very common
Bronchitis	64 (8,2)	common
Herpes zoster	16 (2,0)	common
Tinea versicolor	14 (1,8)	common
Pneumonia	7 (0,9)	uncommon
Neoplasms benign, malignant and unspecified (Incl. cysts and polyps)	14 (1,8)	common
Basal cell carcinoma	1 (0,1)	uncommon
Melanoma	0 (0)	very rare**
Kaposi's sarcoma		
Cardiac Disorders		
Bradycardia	20 (2,6)	common
Nervous system disorders		
Headache	192 (24,5)	very common
Dizziness	69 (8,8)	common
Migraine	45 (5,7)	common
Seizure	7 (0,9)	uncommon
Posterior reversible encephalopathy syndrome (PRES)	0 (0,0)	rare*

Gastrointestinal disorders		
Diarrhoea	99 (12,6)	very common
General disorders and administration site conditions		
Asthenia	15 (1,9)	common
Musculoskeletal and connective tissue disorders		
Back pain	78 (10,0)	very common
Skin and subcutaneous tissue disorders		
Eczema	21 (2,7)	common
Pruritus	21 (2,7)	common
Investigations		
Hepatic enzyme increased (increase ALT, GGT, AST)	119 (15,2)	very common
Blood triglycerides increased	16 (2,0)	common
Respiratory, thoracic and mediastinal disorders		
Cough	96 (12,3)	very common
Dyspnoea	71 (9,1)	common
Eye disorders		
Vision blurred	33 (4,2)	common

Macular oedema	4 (0,5)	uncommon
Vascular disorders		
Hypertension	63 (8,0)	common
Blood and lymphatic system disorders		
Leukopenia	17 (2,2)	common
Lymphopenia	53 (6,8)	common
Thrombocytopenia	0 (0.3)	uncommon

* Not reported in Study FREEDOMS, FREEDOMS II and TRANSFORMS. The frequency category was based on an estimated exposure of approximately 10 000 patients to fingolimod in all clinical trials.

** The frequency category and risk assessment were based on an estimated exposure of more than 24 000 patients to fingolimod 0,5 mg in all clinical trials.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with TUVIGIN via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes.

Immune system disorders

Hypersensitivity reactions, including rash, urticaria and angioedema upon treatment initiation.
Autoimmune haemolytic anaemia

Immune reconstitution inflammatory syndrome (IRIS)

Nervous system disorders

Severe exacerbation of disease after TUVIGIN discontinuation (see section 4.4).

Gastrointestinal disorders

Nausea

Hepatobiliary disorders

Liver injury

Musculoskeletal and connective tissue disorders

Myalgia, arthralgia

Investigations

Weight decreased

c. Description of selected adverse reactions

Infections

In multiple sclerosis clinical trials, the rates of bronchitis, herpes zoster and pneumonia were more common in TUVIGIN treated patients, than in placebo treated patients.

Serious infections occurred at a rate of 1,6 % in the fingolimod 0,5 mg group versus 1,4 % in the placebo group.

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 (see *section 4.4 and 4.5*).

Cryptococcal infections, including isolated cases of cryptococcal meningitis, have been reported in the post- marketing setting (see *section 4.4*).

Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported under treatment with TUVIGIN in the post-marketing setting (see *section 4.4*).

In the post-marketing setting cases of infections with opportunistic pathogens, such as viral (e.g. John Cunningham virus (JCV) causing progressive multifocal leukoencephalopathy (PML), herpes simplex or varicella zoster virus which may lead to meningitis/encephalitis), fungal (e.g. cryptococci causing cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported, some of which have been fatal (see *section 4.4*).

Macular Oedema

In clinical trials, macular oedema occurred in 0,5 % of patients treated with the recommended TUVIGIN dose of 0,5 mg and in 1,1 % of patients treated with the higher 1,25 mg dose.
The majority of cases in multiple sclerosis clinical trials occurred within the first 3 to 4 months of therapy. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmic examination. The macular oedema generally improved or resolved spontaneously after TUVIGIN discontinuation. The risk of recurrence after re-challenge has not been evaluated.

TUVIGIN has not been tested in multiple sclerosis patients with diabetes mellitus. In renal transplant clinical studies where patients with diabetes mellitus were included, therapy with TUVIGIN 2,5 mg and 5 mg resulted in a 2-fold increase in the incidence of macular oedema. Multiple sclerosis patients with diabetes mellitus are therefore expected to be at a higher risk for macular oedema (see *section 4.4*).

Bradydysrhythmia

Initiation of TUVIGIN treatment results in a transient decrease in heart rate and may also be associated with atrio-ventricular conduction delays (see *section 4.4*).

In multiple sclerosis clinical trials the mean maximal decrease in heart rate after the first dose intake was seen 4 to 5 hours post-dose, with declines in mean heart rate, as measured by pulse, of 8 beats per minute for TUVIGIN 0,5 mg. The second dose may result in a slight further decrease. Heart rates below 40 beats per minute have been observed in patients on TUVIGIN 0,5 mg. Heart rate returned to baseline within 1 month of chronic dosing.

In the multiple sclerosis clinical program first-degree atrio-ventricular block (prolonged PR interval on electrocardiogram) was detected following medicine initiation in 4,7 % of patients on TUVIGIN 0,5 mg, in 2,8 % of patients on intramuscular interferon beta-1a IM and in 1,6 % of patients on placebo. Second degree atrio- ventricular block were detected in less than 0,2 % patients on TUVIGIN 0,5 mg.
The conduction abnormalities were typically transient, asymptomatic and resolved within 24 hours on treatment. Although most patients did not require medical intervention one patient on the 0,5 mg dose received isoprenaline for an asymptomatic second degree atrio-ventricular block.

In the post-marketing setting, reports of transient, complete AV block have been observed during the six hour observation period following the first dose of TUVIGIN.

In the post-marketing setting, delayed onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. These cases have been confounded by concomitant medications and/or pre-existing disease. The relationship of such events to TUVIGIN is uncertain.

Blood pressure

In multiple sclerosis clinical trials TUVIGIN 0,5 mg was associated with a mild increase of approximately 1 mmHg on average in mean arterial pressure manifesting after approximately 1 month of treatment initiation. This increase persisted with continued treatment. Hypertension was reported in 6,5 % of patients on TUVIGIN 0,5 mg and in 3,3 % of patients on placebo.

Liver function

Increased hepatic enzymes (mostly ALT elevation) have been reported in multiple sclerosis patients treated with TUVIGIN. In clinical trials, 8,0 % and 1,8 % of patients treated with TUVIGIN 0,5 mg experienced asymptomatic elevation in serum levels of ALT of ≥ 3x ULN and ≥ 5x ULN, respectively, compared with corresponding figures in the placebo group of 1,9 % and 0,9 % respectively. The majority of elevations occurred within 6 to 9 months. ALT levels returned to normal within approximately 2 months after discontinuation of TUVIGIN. In the few patients who experienced ALT elevations of ≥ 5 x ULN and who continued on TUVIGIN therapy, the ALT levels returned to normal within approximately 5 months (see *section 4.4*).

Respiratory System

Minor dose-dependent reductions in forced expiratory volume in 1 second (FEV1) and in the diffusing capacity of the lung for carbon monoxide (DLCO) values were observed with TUVIGIN treatment starting at month 1 and remaining stable thereafter. At month 24, the reduction from baseline values in percent of predicted FEV1 was 2,7 % for TUVIGIN 0,5 mg and 1,2 % for placebo, a difference that resolved after treatment discontinuation.

For DLCO the reductions at month 24 were 3,3 % for TUVIGIN 0,5 mg and 2,7 % for placebo.

Vascular events

Cases of ischaemic and haemorrhagic strokes have been reported at the 0,5 mg dose in clinical trials and in the post-marketing setting.

In Phase III clinical trials, cases of peripheral arterial occlusive disease occurred in patients treated with TUVIGIN at higher doses (1,25 or 5,0 mg).

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.

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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.

TUVIGIN 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 TUVIGIN 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 *section 4.2* and *4.4*).

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

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.

Immune system

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 Side effects). 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 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 to 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-polarceramide 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 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 ($t_{½}$) 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 dysfunction

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 dysfunction

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 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 28 %. 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 suggest that the fingolimod dose does not need to be adjusted in mild or moderate hepatic impairment patients (Child-Pugh class A and B). Fingolimod should be used with caution in patients with severe hepatic impairment (Child-Pugh Class C).

Paediatrics

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

Geriatrics

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, magnesium stearate, titanium dioxide, gelatin

Contains mannitol and may have a laxative effect.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C, protect from moisture

TUVIGIN 0,5 mg capsules must always be stored in the blister to protect from moisture and only removed immediately before use. The blisters should be kept in the carton until required for use.

Keep out of the reach of children.

6.5 Nature and contents of container

7 or 14 capsules per blister made of PVC/PVDC with aluminium foil (Duplex), consisting of a transparent laminated plastic film made of polyvinyl chloride (PVC) and polyvinylidene chloride (PVDC). The aluminium foil is silver and the PVC/PVDC is clear, colourless and transparent. The outer container is a printed cardboard box.

Pack sizes are 7, 28 or 98. Not all pack sizes might be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

TUVIGIN 0,5 mg capsules: 46/34/0023

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