Domilo should be used only by neurologists experienced in the treatment of multiple sclerosis. Domilo 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

Domilo, 0,5 mg (hard capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Domilo is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

Hard gelatine capsule of 16 mm (size 3), with a white body and yellow coloured cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Domilo 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 Domilo is one 0,5 mg capsule taken once daily. If a dose is missed treatment should be continued with the next dose as planned.

On initiation of Domilo 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 Domilo, see section 4.4: Prior treatment with immunosuppressive or immune-modulating therapies.

Dosing in special populations

Renal impairment

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

Hepatic Impairment

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

Elderly patients

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

Diabetic patients

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

Paediatric patients

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

Method of administration

For oral use, with or without food.

4.3 Contraindications

- Hypersensitivity to fingolimod or to any of the excipients listed in section 6.1 (see sections 4.4 and 4.8).
- Concomitant administration with anti-dysrhythmic medicines; Class 1a (e.g. quinidine, procainamide), Class III (e.g. amiodarone, sotalol) (see section 4.4.).
- Pregnancy and lactation.
- Immunodeficiency syndrome.
- Severe active infections, active chronic infections (hepatitis, tuberculosis).
- Active malignancies.

- Patients who in the last 6 months had myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure (see section 4.4).
- 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 wear a pacemaker (see section 4.4).
- Patients with a baseline QTc interval ≥ 500 msec (see section 4.4).

4.4 Special warnings and precautions for use

Bradydysrhythmia

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

After the first dose, the decline in heart rate starts within one hour, and is maximal within 6 hours and usually normalises by one month. However individual patients may not return to baseline heart rate by the end of the first month. Conduction abnormalities were typically transient and asymptomatic. They usually did not require treatment and resolved within the first 24 hours on treatment. If necessary, the decrease in heart rate induced by Domilo can be reversed by parenteral doses of atropine or isoprenaline.

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

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

Should post-dose bradydysrhythmia-related symptoms occur, appropriate clinical management should be initiated, and monitoring should be continued until the symptoms have resolved. Should a patient require pharmacological intervention during the first-

dose monitoring, overnight monitoring in a medical facility should be instituted and the

first-dose monitoring should be repeated after the second dose of Domilo.

If the heart rate at 6 hours is the lowest since the first dose was administered (suggesting that the maximum pharmacodynamic effect on the heart may not yet be manifest), monitoring should be extended by at least 2 hours and until heart rate increases again. Additionally, if after 6 hours, the heart rate is <45 bpm in adults, <55 bpm in paediatric

patients aged 12 years and above, or <60 bpm in paediatric patients aged 10 to below 12 years, or the ECG shows new onset second degree or higher grade AV block or a QTc interval ≥500 msec, extended monitoring (at least overnight monitoring), should be performed, and until the findings have resolved. The occurrence at any time of third degree AV block should also lead to extended monitoring (at least overnight monitoring).

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

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

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

Cases of T-wave inversion have been reported in adult patients treated with fingolimod as contained in Domilo. In case of T-wave inversion, the medical practitioner should ensure that there are no associated myocardial ischaemia signs or symptoms. If myocardial ischaemia is suspected, it is recommended to seek advice from a cardiologist.

Due to the risk of serious rhythm disturbances or significant bradycardia, Domilo should not be used in patients with sino-atrial heart block, a history of symptomatic bradycardia, recurrent syncope or cardiac arrest, or in patients with significant QT prolongation (QTc>470 msec [adult female], QTc >460 msec [paediatric female] or >450 msec [adult and paediatric male]), uncontrolled hypertension or severe sleep apnoea (see also section 4.3). If treatment is considered in patients for whom Domilo is not contradicted, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy. At least overnight extended monitoring is recommended for treatment initiation (see also section 4.5).

Domilo has not been studied in patients with dysrhythmias requiring treatment with class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) anti-dysrhythmic medicines. Class Ia and class III anti-dysrhythmic medicines have been associated with cases of torsades de pointes in patients with bradycardia (see section 4.3). Since initiation of Domilo treatment results in decreased heart rate, Domilo should not be co-administered with these medicines.

Experience with Domilo is limited in patients receiving concurrent therapy with beta blockers, heart-rate-lowering calcium channel blockers (such as verapamil or diltiazem), or other substances which may decrease heart rate (e.g. ivabradine, digoxin, anticholinesteratic medicines or pilocarpine). Since the initiation of Domilo treatment is also associated with slowing of the heart rate (see also section 4.8, Bradydysrhythmia), concomitant use of these medicines during Domilo initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate treatment with Domilo should not be initiated in patients who are concurrently treated with these medicines (see section 4.5). If treatment with Domilo 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).

QT interval

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

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

Immunosuppressive effects

Domilo has an immunosuppressive effect that predisposes patients to an infection risk, including opportunistic infections that can be fatal, and increases the risk of developing lymphomas and other malignancies, particularly those of the skin. Medical practitioners should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the medical practitioner on a case-by-case basis (see also section 4.4 “Infections” and “Cutaneous neoplasms” and section 4.8 “Lymphomas”). Use with caution in patients with HIV and tuberculosis.

Infections

Domilo causes a dose-dependent reduction of the peripheral lymphocyte count to

20-30 % of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues (see section 5.1).

Before initiating treatment with Domilo, a recent full blood count (FBC) (i.e. within 6 months or after discontinuation of prior therapy) should be available. Assessments of FBC are also recommended periodically during treatment, at month 3 and at least yearly thereafter, and in case of signs of infection. Absolute lymphocyte count <0,2x10^9/l, if confirmed, should lead to treatment interruption until

recovery, because in clinical studies, fingolimod treatment was interrupted in patients with absolute lymphocyte count <0,2x10^9/l.

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

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

The immune system effects of Domilo may increase the risk of infections, including opportunistic infections (see section 4.8). Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. When evaluating a patient with a suspected infection that could be serious, referral to a medical practitioner experienced in treating infections should be considered. During treatment, patients receiving Domilo should be instructed to report promptly symptoms of infection to their medical practitioner.

Suspension of Domilo should be considered if a patient develops a serious infection and consideration of benefit-risk should be undertaken prior to re-initiation of therapy.

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

Cases of progressive multifocal leukoencephalopathy (PML) has been reported under Domilo treatment since marketing authorisation (see section 4.8). PML is an opportunistic infection caused by John Cunningham virus (JCV), which may be fatal or result in severe disability. Cases of PML have occurred after approximately 2-3 years of monotherapy treatment without previous exposure to natalizumab, although an exact relationship with the duration of treatment is unknown. Additional PML cases have occurred in patients who had been treated previously with natalizumab, which has a known association with PML. PML can only occur in the presence of a JCV infection. If JCV testing is undertaken, it should be considered that the influence of lymphopenia on the accuracy of anti-JCV antibody testing has not been studied in fingolimod-treated patients. It should also be noted that a negative anti-JCV antibody test does not preclude the possibility of subsequent JCV infection. Before initiating treatment with Domilo, a baseline MRI should be available (usually within 3 months) as a reference. Medical practitioners should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI may be considered as part of increased vigilance in patients considered at increased risk of PML. Cases of asymptomatic PML based on MRI findings and positive JCV DNA in the cerebrospinal fluid

have been reported in patients treated with fingolimod. If PML is suspected, MRI should be performed immediately for diagnostic purposes and treatment with Domilo should be discontinued until the PML has been excluded.

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

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

Macular oedema

Macular oedema with or without visual symptoms has been reported in 0,5 % of patients treated with fingolimod 0,5 mg as contained in Domilo, occurring predominantly in the first 3-4 months of therapy (see section 4.8). An ophthalmological evaluation is therefore recommended at 3-4 months after treatment initiation. If patients report visual disturbances at any time while on 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). Domilo has not been studied in multiple sclerosis patients with concomitant diabetes mellitus. It is recommended that multiple sclerosis patients with diabetes mellitus or a history

of uveitis undergo an ophthalmological evaluation prior to initiating therapy and have follow-up evaluations while receiving therapy.

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

Liver function

Increased hepatic enzymes, mostly alanine aminotransaminase (ALT) but also gamma glutamyltransferase (GGT) and aspartate transaminase (AST) 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 and the medicine was discontinued if the elevation exceeded a 5-fold increase. Recurrence of liver transaminase elevations occurred with re-challenge in some patients, supporting a relationship to the medicine. In clinical studies, transaminase elevations occurred at any time during treatment although the majority occurred within the first 12 months. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of fingolimod.

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

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

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have liver enzymes checked and Domilo should be discontinued if significant liver injury is confirmed (for example liver transaminase levels greater than 5-fold the ULN and/or serum bilirubin elevations). Resumption of therapy will be dependent on whether or not another cause of liver injury is determined and on the benefits to patient of resuming therapy versus the risks of recurrence of liver dysfunction.

Although there are no data to establish that patients with pre-existing liver disease are at increased risk of developing elevated liver function tests when taking Domilo.

Domilo should be used with caution in patients with a history of significant liver disease.

Interference with serological testing

Since fingolimod as contained in Domilo, 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 Domilo. Laboratory tests involving the use of

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

Blood pressure effects

Patients with hypertension uncontrolled by medication were excluded from participation in premarketing clinical trials and special care is indicated if patients with uncontrolled hypertension are treated with Domilo.

Hypertension was reported as an adverse event and therefore blood pressure should be regularly monitored during treatment with Domilo.

Respiratory effects

Minor dose-dependent reductions in values for forced expiratory volume (FEV1) and diffusion capacity for carbon monoxide (DLCO) were observed with Domilo treatment starting at month 1 and remaining stable thereafter. Domilo should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease (see also section 4.8).

Posterior reversible encephalopathy syndrome

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported at the 0,5 mg dose in reported 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, Domilo should be discontinued.

Prior treatment with immunosuppressive or immunomodulatory therapies

There were no studies performed to evaluate the efficacy and safety of Domilo when switching patients from teriflunomide, dimethyl fumarate or alemtuzumab treatment to Domilo. When switching patients from another disease modifying therapy to Domilo, 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 the risk of disease reactivation. A recent complete blood cell count is recommended prior to initiating Domilo to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.

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

For dimethyl fumarate, the washout period should be sufficient for FBC to recover before treatment with Domilo is started.

Due to the long half-life of natalizumab, elimination usually takes up to 2-3 months following discontinuation. Teriflunomide is also eliminated slowly from the plasma. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take from several months up to 2 years. An accelerated elimination procedure as defined in the teriflunomide professional information is recommended or alternatively washout period should not be shorter than 3,5 months. Caution regarding

potential concomitant immune effects is required when switching patients from natalizumab or teriflunomide to Domilo.

Alemtuzumab has profound and prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with Domilo after alemtuzumab is not recommended.

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

Co-administration with potent CYP450 inducers

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

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 Domilo (see section 4.8).

Vigilance for skin lesions is warranted and a medical evaluation of the skin is recommended at initiation, and then every 6 to 12 months taking into consideration clinical judgement. The patient should be referred to a dermatologist in case suspicious lesions are detected.

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

Lymphomas

There have been cases of lymphoma in clinical studies and the post-marketing setting (see section 4.8). 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. A fatal case of Epstein-Barr virus (EBV) positive B-cell lymphoma has also been observed. If lymphoma is suspected, Domilo should be discontinued.

Tumefactive lesions

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 Domilo should be considered by the medical practitioner on a case-by-case basis taking into account individual benefits and risks.

Return of disease activity (rebound)

Cases of severe exacerbation of disease have been reported after stopping Domilo in the post-marketing setting. The possibility of recurrence of exceptionally high disease activity should be considered (see "Stopping therapy" below).

Stopping therapy

If a decision is made to stop treatment with Domilo a 6-week interval without therapy is needed, based on half-life, to clear fingolimod from the circulation (see section 5.2). Lymphocyte counts progressively return to normal range within 1-2 months of stopping therapy in most patients (see section 5.1) although full recovery can take significantly longer in some patients. Starting other therapies during this interval will result in concomitant exposure to Domilo. Use of immunosuppressants soon after the discontinuation of Domilo may lead to an additive effect on the immune system and caution is therefore indicated.

Caution is also indicated when stopping Domilo therapy due to the risk of a rebound (see "Return of disease activity (rebound)" above). If discontinuation of Domilo is deemed necessary, patients should be monitored during this time for relevant signs of a possible rebound.

Paediatric population

Domilo is not indicated for use in paediatric patients.

4.5 Interaction with other medicines and other forms of interaction

Anti-neoplastic, immunomodulatory or immunosuppressive therapies

Anti-neoplastic, immunomodulatory or immunosuppressive therapies should be co-administered with caution due to the risk of additive immune system effects (see sections 4.4).

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

Vaccination

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

Bradycardia-inducing medicines

Treatment with Domilo should not be initiated in patients receiving beta blockers, or other medicines which may decrease heart rate, such as class Ia and III anti-dysrhythmics, calcium channel blockers (such as verapamil or diltiazem), ivabradine, digoxin, anti-cholinesteratic medicines or pilocarpine because of the potential additive effects on heart rate (see sections 4.4 and 4.8). If treatment with Domilo is considered in such patients, advice from a cardiologist should be sought regarding the switch to non-heart rate lowering medicines or appropriate monitoring for treatment initiation, at least overnight monitoring is recommended.

Pharmacokinetic interactions of other medicines on fingolimod

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

Co-administration of carbamazepine 600 mg twice daily at steady-state and a single dose of Domilo 2 mg reduced the AUC of fingolimod and its metabolite by approximately 40 %. Other strong CYP3A4 enzyme inducers, for example rifampicin, phenobarbitone, phenytoin, efavirenz and St. John's Wort, may reduce the AUC of fingolimod and its metabolite at least to this extent. As this could potentially impair the efficacy, their co-administration should be used with caution. Concomitant administration with St. John's Wort is however not recommended (see section 4.4).

Pharmacokinetic interactions of fingolimod on other medicines

Domilo is unlikely to interact with *medicines* mainly cleared by the CYP450 enzymes or by substrates of the main transporter proteins.

Co-administration of Domilo with ciclosporin did not elicit any change in the ciclosporin or fingolimod exposure. Therefore, Domilo is not expected to alter the pharmacokinetics of medicines that are CYP3A4 substrates.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in females

Due to risk to the foetus, Domilo is contraindicated during pregnancy and in women of childbearing potential not using effective contraception.

Before initiation of treatment in women of childbearing potential, a negative pregnancy test result needs to be available and counselling should be provided regarding the potential for serious risk to the foetus and the need for effective contraception during treatment with Domilo. Since it takes approximately two months to eliminate fingolimod from the body on stopping treatment (see section 4.4), the potential risk to the foetus may persist and contraception should be continued during that period.

Pregnancy

Domilo should not be used in pregnancy (see section 4.3). Animal studies have shown reproductive toxicity including foetal loss and organ defects, notably persistent truncus arteriosus and ventricular septal defect (see section 5.3). Furthermore, the receptor affected by fingolimod (sphingosine 1-phosphate receptor) is known to be involved in vascular formation during embryogenesis.

Safety in pregnancy and lactation has not been established.

Breastfeeding

Fingolimod is excreted in milk of treated animals during lactation (see section 5.3).

Women receiving Domilo should not breastfeed.

Fertility

Fingolimod is present in seminal ejaculate. Safety regarding an increased risk of male mediated foetal toxicity has not been demonstrated.

4.7 Effects on ability to drive and use machines

The clinical status of the patient and adverse event profile of Domilo 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

Adverse reactions reported with fingolimod in clinical studies are shown below. Adverse reactions derived from post-marketing experience with fingolimod via spontaneous case reports or literature cases are also reported in table below.

b. Tabulated list of adverse reactions

MedDRA SOC	
Infections and infestations	
Frequent	Influenza, sinusitis, Herpes viral infections, bronchitis, tinea versicolor

Less frequent	Pneumonia
Unknown frequency	Progressive multifocal leukoencephalopathy (PML)**, cryptococcal infections**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Frequent	Basal cell carcinoma
Less frequent	Malignant melanoma****, lymphoma***, squamous cell carcinoma****, kaposi's sarcoma****
Unknown frequency	Merkel cell carcinoma***
Blood and lymphatic system disorders	
Frequent	Lymphopenia, leucopenia
Less frequent	Thrombocytopenia
Unknown frequency	Autoimmune haemolytic anaemia***, peripheral oedema***
Immune system disorders	
Unknown frequency	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)*
Unknown frequency	Severe exacerbation of disease after Domilo discontinuation***
Eye disorders	
Frequent	Blurred vision

Less frequent	Macular oedema
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***
Skin and subcutaneous tissue disorders	
Frequent	Eczema, alopecia, pruritus
Musculoskeletal and connective tissue disorders	
Frequent	Back pain, myalgia, arthralgia
General disorders and administration site conditions	
Frequent	Asthenia
Investigations	
Frequent	Increased hepatic enzyme (increased ALT, Gamma glutamyltransferase, Aspartate transaminase), decreased weight***, increased blood triglycerides
Less frequent	Decreased neutrophil count

* Not reported in reports from studies 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.

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

*** Adverse drug reactions from spontaneous reports and literature.

**** 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 reported clinical trials.

c. Description of selected adverse reactions

Infections

In multiple sclerosis clinical studies the rates of lower respiratory tract infections, primarily bronchitis and to a lesser extent herpes infection and pneumonia were more frequent in Domilo-treated patients than in placebo treated patients.

Some cases of disseminated herpes infection, including fatal cases, have been reported even at the 0,5 mg dose.

In the post-marketing setting, cases of infections with opportunistic pathogens, such as viral (e.g. varicella zoster virus [VZV], John Cunningham virus [JCV] causing Progressive Multifocal Leukoencephalopathy, herpes simplex virus [HSV]), fungal (e.g. cryptococci including cryptococcal

meningitis) or bacterial (e.g. atypical mycobacterium), have been reported, some of which have been fatal (see section 4.4).

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.

Macular oedema

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

Macular oedema incidence is increased in multiple sclerosis patients with a history of uveitis (17 % with a history of uveitis vs. 0,6 % without a history of uveitis). Domilo has not been studied in multiple sclerosis patients with diabetes mellitus, a disease which is associated with an increased risk for macular oedema (see section 4.4). In renal transplant clinical studies in which patients with diabetes mellitus were included, therapy with fingolimod 2,5 mg and 5 mg resulted in a 2-fold increase in the incidence of macular oedema.

Bradydysrhythmia

Initiation of Domilo treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays.

It has been reported that in multiple sclerosis clinical studies the maximal decline in heart rate was seen within 6 hours after treatment initiation, with declines in mean heart rate of 12-13 beats per minute for Domilo. Heart rate below 40 beats per minute in adults, and below 50 beats per minute in paediatric patients, was observed in patients on Domilo. The average heart rate returned towards baseline within 1 month of chronic treatment. Bradycardia was generally asymptomatic, but some patients experienced mild to moderate symptoms, including hypotension, dizziness, fatigue and/or palpitations, which resolved within the first 24 hours after treatment initiation (see sections 4.4 and 5.1).

Reports from multiple sclerosis clinical studies have shown first-degree atrioventricular block (prolonged PR interval on ECG) after treatment initiation in adult and paediatric patients. It has been reported that in clinical trials involving adults it occurred in 4,7 % of patients on fingolimod 0,5 mg, in 2,8 % of patients on intramuscular interferon beta-1a, and in 1,6 % of patients on placebo. Second-degree atrioventricular block was detected in less than 0,2 % adult patients on Domilo. In the post-marketing setting, reports of transient, spontaneously resolving complete AV block have been observed during the six-hour monitoring period following the first dose of Domilo. The patients recovered spontaneously. The conduction abnormalities observed both in clinical trials and post-marketing were typically transient, asymptomatic and resolved within the first 24 hours after treatment initiation. Although most patients did not require medical intervention, one patient on fingolimod 0,5 mg received isoprenaline for asymptomatic second-degree Mobitz I atrioventricular block.

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 Domilo is uncertain.

Blood pressure

It has been reported that in multiple sclerosis clinical trials Domilo was associated with an average increase of approximately 3 mmHg in systolic pressure and approximately 1 mmHg in diastolic pressure, manifesting approximately 1 month after treatment initiation. This increase persisted with continued treatment. Hypertension was reported in 6,5 % of patients on treatment and in 3,3 % of patients on placebo.

Liver function

Increased hepatic enzymes have been reported in adult and paediatric multiple sclerosis patients treated with Domilo. In clinical studies 8,0 % and 1,8 % of adult patients treated with Domilo experienced an asymptomatic elevation in serum levels of ALT of ≥3x ULN (upper limit of normal) and ≥5x ULN, respectively. Recurrence of liver transaminase elevations has occurred upon re-challenge in some patients, supporting a relationship to the medicine. In clinical studies, transaminase elevations occurred at any time during treatment although the majority occurred within the first 12 months. ALT levels returned to normal within approximately 2 months after discontinuation of Domilo. In a small number of patients (N=10 on 1,25 mg, N=2 on 0,5 mg) who experienced ALT elevations ≥5x ULN and who continued on Domilo therapy, the ALT levels returned to normal within approximately 5 months (see section 4.4, Liver function).

Nervous system disorders

Reports from clinical studies have shown that events involving the nervous system occurred in patients treated with fingolimod at higher doses (1,25 or 5,0 mg) including ischaemic and haemorrhagic strokes and neurological atypical disorders, such as acute disseminated encephalomyelitis (ADEM)-like events.

Cases of seizures, including status epilepticus, have been reported in clinical studies and in the post-marketing setting.

Vascular disorders

Cases of peripheral arterial occlusive disease occurred in patients treated with Domilo at higher doses (1,25 mg).

Respiratory system

Minor dose-dependent reductions in values for forced expiratory volume (FEV_1) and diffusion capacity for carbon monoxide (DLCO) were observed with Domilo treatment starting at month 1 and remaining stable thereafter. At month 24, the reduction from baseline values in percentage of predicted FEV1 was 2,7 % for fingolimod 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 fingolimod 0,5 mg and 2,7 % for placebo.

Lymphomas

There have been cases of lymphoma of different varieties, in both clinical studies and the post-marketing setting, including a fatal case of Epstein-Barr virus (EBV) positive B-cell lymphoma. The incidence of lymphoma (B-cell and T-cell) cases was higher in clinical trials than expected in the general population. Some T-cell lymphoma cases were also reported in the post-marketing setting, including cases of cutaneous T-cell lymphoma (mycosis fungoides).

Haemophagocytic syndrome

Cases of haemophagocytic syndrome (HPS) with fatal outcome have been reported in patients treated with fingolimod such as Domilo in the context of an infection. HPS is a rare condition that has been described in association with infections, immunosuppression and a variety of autoimmune diseases.

d. Paediatric population

Mild isolated bilirubin increases have been noted in paediatric patients on fingolimod.

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 providers 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, 5 of 6 subjects reported mild chest tightness or discomfort which was clinically consistent with bronchoconstriction.

Domilo 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 sections 4.4 and 4.8).

If the overdose constitutes first exposure to Domilo 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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 34 Other: selective immunosuppressive medicines

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.

Pharmacodynamic effects

Immune system

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 minimal count of approximately 500 cells/µl or approximately 30 % of baseline. Eighteen percent of patients reached a minimal count 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 a transient reduction in heart rate and decrease in atrioventricular conduction at treatment initiation (see sections 4.4 and 4.8). The maximal decline in heart rate is seen within 6 hours post dose, with 70 % of the negative chronotropic effect achieved on the first day. With continued administration heart rate returns to baseline within one month. The decrease in heart rate induced by fingolimod can be reversed by parenteral doses of atropine or isoprenaline. Inhaled salmeterol has also been shown to have a modest positive chronotropic effect. 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. Autonomic responses of the heart, including diurnal variation of heart rate and response to exercise are not affected by fingolimod treatment.

S1P4 could partially contribute to the effect but was not the main receptor responsible for the lymphoid depletion. The mechanism of action of bradycardia and vasoconstriction were also studied *in vitro* in guinea pigs and isolated rabbit aorta and coronary artery. It was concluded that bradycardia could be mediated primarily by activation of inward rectifying potassium channel or G-protein activated inwardly rectifying K+ channel (IKACh/GIRK) and that vasoconstriction seems to be mediated by a Rho kinase and calcium dependent mechanism.

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 rate (FEF) 25-75. 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 beta-agonists.

5.2 Pharmacokinetic properties

Absorption

Fingolimod absorption is slow (t_{max} of 12-16 hours) and extensive (≥85 %). The apparent absolute oral bioavailability is 93 % (95 % confidence interval: 79-111 %). Steady-state-blood concentrations are reached within 1 to 2 months following once-daily administration and steady-state levels are approximately 10-fold greater than with the initial dose.

Food intake does not alter C_{max} or exposure (AUC) of fingolimod. Fingolimod phosphate C_{max} was slightly decreased by 34 % but AUC was unchanged. Therefore, Domilo may be taken without regard to meals (see section 4.2).

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 %). Fingolimod and fingolimod-phosphate protein binding is not altered by renal or hepatic impairment. Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1 200 ± 260 litres. 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 6-9 days. Blood levels of fingolimod and fingolimod phosphate decline in parallel in the terminal phase, leading to 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 apparently dose proportional manner after multiple once-daily doses of 0,5 mg or 1,25 mg.

Characteristics in specific groups of subjects or patients

The pharmacokinetics of fingolimod and fingolimod phosphate do not differ in males and females, in patients of different ethnic origin, or in patients with mild to severe renal impairment.

Renal dysfunction

Severe renal impairment increases fingolimod Cmax 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

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

Fingolimod should be used with caution in patients with severe hepatic impairment (Child-Pugh class C) (see section 4.3).

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

Paediatric population

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

Elderly

Clinical experience and pharmacokinetic information in patients aged above 65 years are limited. Domilo should be used with caution in patients aged 65 years and over (see section 4.2).

5.3 Preclinical safety data

The preclinical safety profile of fingolimod was assessed in mice, rats, dogs and monkeys. The major target organs were the lymphoid system (lymphopenia and lymphoid atrophy), lungs (increased weight, smooth muscle hypertrophy at the bronchio-alveolar junction), and heart (negative chronotropic effect, increase in blood pressure, perivascular changes and myocardial degeneration) in several species; blood vessels (vasculopathy) in rats only at doses of 0,15 mg/kg and higher in a 2-year study, representing an approximate 4-fold margin based on the human systemic exposure (AUC) at a daily dose of 0,5 mg.

No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of fingolimod up to the maximally tolerated dose of 2,5 mg/kg, representing an approximate 50-fold margin based on human systemic exposure (AUC) at the 0,5 mg dose. However, in a 2-year mouse study, an increased incidence of malignant lymphoma was seen at doses of 0,25 mg/kg and higher, representing an approximate 6-fold margin based on the human systemic exposure (AUC) at a daily dose of 0,5 mg.

Fingolimod was neither mutagenic nor clastogenic in animal studies.

Fingolimod had no effect on sperm count/motility or on fertility in male and female rats up to the highest dose tested (10 mg/kg), representing an approximate 150-fold margin based on human systemic exposure (AUC) at a daily dose of 0,5 mg.

Fingolimod was teratogenic in the rat when given at doses of 0.1 mg/kg or higher. Drug exposure in rats at this dose was similar to that in patients at the therapeutic dose (0,5 mg). The most common foetal visceral malformations included persistent truncus arteriosus and ventricular septum defect. The teratogenic potential in rabbits could not be fully assessed, however an increased embryo-foetal mortality was seen at doses of 1,5 mg/kg and higher, and a decrease in viable foetuses as well as foetal growth retardation was seen at 5 mg/kg. Drug exposure in rabbits at these doses was similar to that in patients.

In rats, F1 generation pup survival was decreased in the early postpartum period at doses that did not cause maternal toxicity. However, F1 body weights, development, behaviour, and fertility were not affected by treatment with fingolimod.

Fingolimod was excreted in milk of treated animals during lactation at concentrations 2-fold to 3-fold higher than that found in maternal plasma. Fingolimod and its metabolites crossed the placental barrier in pregnant rabbits.

Juvenile animal studies

Results from two toxicity studies in juvenile rats showed slight effects on neurobehavioural response, delayed sexual maturation and a decreased immune response to repeated stimulations with keyhole limpet haemocyanin (KLH), which were not considered adverse. Overall, the treatment-related effects of fingolimod in juvenile animals were comparable to those seen in adult rats at similar dose levels, with the exception of changes in bone mineral density and neurobehavioural impairment (reduced auditory startle response) observed at doses of 1,5 mg/kg and higher in juvenile animals and the absence of smooth muscle hypertrophy in the lungs of the juvenile rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill

Magnesium stearate

Potassium citrate

Silica, colloidal anhydrous

Capsule composition

Hard gelatine capsules (Size 3)

Capsule body

Gelatine

Titanium dioxide (E171)

Capsule cap

Gelatine

Titanium dioxide (E171)

Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the capsule in the blister in the outer carton until required for use.

6.5 Nature and contents of container

The capsules are packed into oPA/Al/PVC/Al (Al/Al 45) blisters (in a carton box).

7 capsules per blister. The outer container is a printed cardboard box.

Available pack sizes: 7, 28 or 98 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand

1685

South Africa

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

To be allocated.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated.

10. DATE OF REVISION OF THE TEXT