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

Filengia, 0,5 mg (capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Filengia is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

Hard gelatine capsule (size 4), filled with white to off-white powder with small agglomerates. Capsule body:

white opaque with TV 7820 imprinted. Capsule cap: yellow with TV 7820 imprinted.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Filengia 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 Filengia 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 Filengia 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 Filengia, see section 4.4: Prior treatment with immunosuppressive or immune-modulating therapies.

Dosing in special populations

Renal impairment

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

Hepatic Impairment

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

Paediatric patients

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

Elderly patients

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

Diabetic patients

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

Method of administration

For oral use

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 Ia (e.g., quinidine, procainamide, disopyramide), Class III (e.g. amiodarone, sotalol) (see section 4.4.).
- 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).
- Pregnancy and lactation.

- 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

Bradydysrhythmia

Initiation of Filengia treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays, including the occurrence of isolated reports of transient, spontaneously resolving complete AV block (see sections 4.3, 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 Filengia 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 Filengia. 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 Filengia.

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, 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 Filengia treatment depending on duration of the interruption and time since start of Filengia 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 Filengia. In case of T-wave inversion, the prescriber should ensure that there are no associated myocardial ischaemia signs or symptoms. If myocardial ischaemia is suspected, it is recommended to seek advice from a cardiologist.

Due to the risk of serious rhythm disturbances or significant bradycardia, Filengia 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], or >450 msec [adult male]), uncontrolled hypertension or severe sleep apnoea (see also section 4.3). In such patients, if treatment with

Filengia is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring. At least overnight extended monitoring is recommended for treatment initiation (see also section 4.5).

Filengia has not been studied in patients with dysrhythmias requiring treatment with class Ia (e.g. quinidine, procainamide, 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.

Since initiation of Filengia treatment results in decreased heart rate, Filengia should not be co-administered with these medicines (see section 4.3)

Experience with Filengia 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 Filengia treatment is also associated with slowing of the heart rate (see also section 4.8, Bradydysrhythmia), concomitant use of these medicines during Filengia initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate treatment with Filengia should not be initiated in patients who are concurrently treated with these medicines (see also section 4.5). If treatment with Filengia 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, hypomagnesaemia or congenital QT prolongation.

Immunosuppressive effects

Filengia 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”).

Infections

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

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

***Filengia therapy*).**

Patients need to be assessed for their immunity to varicella (chickenpox) prior to Filengia 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 Filengia therapy. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with Filengia (see section 4.8). Initiation of treatment with Filengia should be postponed for 1 month to allow full effect of vaccination to occur.

The immune system effects of Filengia may increase the risk of infections, including opportunistic infections (see section 4.8). 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 Filengia should be instructed to report promptly symptoms of infection to their medical practitioner.

Suspension of Filengia 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, Filengia should be discontinued and appropriate treatment should be initiated. A multidisciplinary consultation (i.e. infectious disease specialist) should be undertaken if re-initiation of Filengia is warranted.

Cases of progressive multifocal leukoencephalopathy (PML) has been reported under fingolimod, as contained

in Filengia, 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 the estimated risk appears to increase with cumulative exposure over time, 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 Filengia, a baseline MRI should be available (usually within 3 months) as a reference. MRI findings may be apparent before clinical signs or symptoms. During routine MRI (in accordance with national and local recommendations), medical practitioners should pay attention to PML suggestive lesions. 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, as contained in Filengia. If PML is suspected, MRI should be performed immediately for diagnostic purposes and treatment with Filengia should be discontinued until PML has been excluded.

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

Elimination of Filengia 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 Filengia.

Vaccination

Vaccination may be less effective during and for up to two months after stopping treatment with Filengia. The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided (see sections 4.5 and 4.8).

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 Filengia, 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). Filengia 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 Filengia therapy.

Continuation of Filengia in patients with macular oedema has not been evaluated. It is recommended that Filengia be discontinued if a patient develops macular oedema. A decision on whether or not Filengia 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 Filengia. A 3-fold or greater elevation in ALT occurred in 8,0 % of patients treated with Filengia 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 fingolimod, as contained in Filengia. 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, as contained in Filengia.

Due to the immunosuppressive properties of Filengia, 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 Filengia. 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 Filengia 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 Filengia 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 Filengia, Filengia should be used with caution in patients with a history of significant liver disease.

Interference with serological testing

Since fingolimod, as contained in Filengia, 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 Filengia. 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 Filengia.

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

Respiratory effects

Minor dose-dependent reductions in values for forced expiratory volume (FEV1) and diffusion capacity for carbon monoxide (DLCO) were observed with Filengia treatment starting at month 1 and remaining stable thereafter. Filengia 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 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, Filengia should be discontinued.

Prior treatment with immunosuppressive or immunomodulatory therapies

When switching patients from another disease modifying therapy to Filengia, 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 Filengia to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.

Filengia 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 Filengia is started.

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

Alemtuzumab has profound and prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with Filengia 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 Filengia 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 Filengia (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 Filengia 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, Filengia should be discontinued.

Women of childbearing potential

Due to risk to the foetus, fingolimod, as contained in Filengia, is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for 2 months after treatment discontinuation (see sections 4.3 and 4.6).

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 Filengia 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 Filengia in the post-marketing setting. This was generally observed within 12 weeks after stopping Filengia, but was also reported up to and beyond 24 weeks after Filengia discontinuation. 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 Filengia a 6-week interval without therapy is needed, based on half-life, to clear fingolimod, as contained in Filengia, 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 Filengia. Use of immunosuppressants soon after the discontinuation of Filengia may lead to an additive effect on the immune system and caution is therefore indicated.

Caution is also indicated when stopping Filengia therapy due to the risk of a rebound (see "Return of disease

activity (rebound)" above). If discontinuation of Filengia is deemed necessary, patients should be monitored during this time for relevant signs of a possible rebound.

Paediatric population

Filengia 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 not be co-administered due to the risk of additive immune system effects (see sections 4.3 and 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 Filengia 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

Fingolimod, as contained in Filengia, has been studied in combination with atenolol and diltiazem. When fingolimod was used with atenolol in an interaction study in healthy volunteers, there was an additional 15 % reduction of heart rate at fingolimod, as contained in Filengia, treatment initiation, an effect not seen with diltiazem. Treatment with Filengia 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 Filengia 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, if the heart-rate-lowering medication cannot be stopped.

Pharmacokinetic interactions of other substances on fingolimod

Filengia 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, as contained in Filengia, disposition. Co-administration of fingolimod, as contained in Filengia, with ketoconazole resulted in a 1,7-fold increase in fingolimod and fingolimod phosphate exposure (AUC) by inhibition of CYP4F2. Caution should be exercised with substances that may inhibit CYP3A4 (protease inhibitors, azole antifungals, some macrolides such as clarithromycin or telithromycin).

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

Pharmacokinetic interactions of fingolimod on other substances

Fingolimod, as contained in Filengia, is unlikely to interact with substances mainly cleared by the CYP450 enzymes or by substrates of the main transporter proteins.

Co-administration of fingolimod, as contained in Filengia, with ciclosporin did not elicit any change in the

ciclosporin or fingolimod exposure. Therefore, Filengia is not expected to alter the pharmacokinetics of medicines that are CYP3A4 substrates.

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

4.6 Fertility, pregnancy and lactation

Filengia 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 females

Filengia is contraindicated in women of childbearing potential not using effective contraception (see section 4.3). Therefore, before initiation of Filengia 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 Filengia since fingolimod takes approximately 2 months to eliminate from the body after treatment discontinuation (see section 4.4).

When stopping Filengia treatment for planning a pregnancy the possible return of disease activity should be considered (see section 4.4: Return of disease activity (rebound) after Filengia 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

Filengia 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 Filengia should not breastfeed.

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

Filengia has no or negligible influence on the ability to drive and use machines.

Dizziness or drowsiness may occasionally occur when initiating therapy with Filengia. On initiation of Filengia treatment it is recommended that patients be observed for a period of 6 hours (see section 4.4, Bradydysrhythmia).

4.8 Undesirable effects

a. Summary of the safety profile

The most serious adverse reactions reported for the 0,5 mg recommended therapeutic dose were infections,

macular oedema and transient atrio-ventricular blocks on treatment initiation.

The most frequent adverse reactions at the 0,5 mg dose were headache, influenza, diarrhoea, sinusitis, back pain, hepatic enzyme increased and cough. The most frequent reported adverse event for the 0,5 mg dose leading to treatment interruption was ALT elevations.

b. Tabulated list of adverse reactions

MedDRA SOC	
Infections and infestations	
Frequent	Influenza, sinusitis, Herpes zoster, bronchitis, tinea versicolor
Less frequent	Pneumonia
Unknown frequency	Progressive multifocal leukoencephalopathy (PML)**, cryptococcal infections** Varicella Zoster Virus, John Cunningham Virus causing progressive multifocal leukoencephalopathy (PML), herpes simplex virus (HSV), bacterial (e.g., atypical mycobacterium).
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 Filengia 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
Frequency unknown	Ischaemic and haemorrhagic strokes
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

* 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

Lower respiratory tract infections, primarily bronchitis and to a lesser extent herpes infection and pneumonia were reported more frequently in fingolimod, as contained in Filengia, treated patients.

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

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, as contained in Filengia. Due to the immunosuppressive properties of fingolimod, as contained in Filengia, vaccination against HPV should be considered prior to treatment initiation with fingolimod, as contained in Filengia, taking into account vaccination recommendations. Cancer screening, including Pap test, is recommended as per standard of care.

Macular oedema

Macular oedema has been reported at the recommended dose of 0,5 mg. The incidence of macular oedema increased at a higher dose of 1,25 mg. The majority of cases reported occurred within the first 3-4 months of therapy. Blurred vision or decreased visual acuity have been reported. Macular oedema has also been reported in asymptomatic patients during routine ophthalmological examination. Macular oedema generally improved or resolved spontaneously after discontinuation of treatment with fingolimod, as contained in Filengia. The risk of recurrence after re-challenge has not been evaluated.

A higher incidence of macular oedema has been reported in multiple sclerosis patients with a history of uveitis. The increased risk for macular oedema in patients with diabetes mellitus has not been studied (see section 4.4). A 2-fold increase in the incidence of macular oedema has been reported at a dose of 2,5 mg and 5 mg in renal transplant patients, including patients with diabetes mellitus.

Bradydysrhythmia

A transient decrease in heart rate which may also be associated with atrioventricular conduction delays has been reported at initiation of treatment with fingolimod, as contained in Filengia.

Maximal decline in heart rate has been reported within 6 hours after treatment initiation with fingolimod, as contained in Filengia, with declines in mean heart rate of 12-13 beats per minute. Heart rate below 40 beats per minute in adults, has been observed less frequently in patients treated with fingolimod, as contained in Filengia. The average heart rate returns towards baseline within 1 month of chronic treatment. Bradycardia is generally

asymptomatic. Mild to moderate symptoms, including hypotension, dizziness, fatigue and/or palpitations have been reported. These symptoms resolve within 24 hours after initiation of treatment (see sections 4.4 and 5.1).

First-degree atrioventricular block (prolonged PR interval on ECG) has been detected and reported after treatment initiation in adult patients. Second-degree atrioventricular block has been reported in adults at a dose of 0,5 mg. Less frequent reports of transient, spontaneously resolving complete AV block have been observed during the six-hour monitoring period following the first dose of fingolimod, as contained in Filengia. The conduction abnormalities reported were typically transient, asymptomatic and resolved within the first 24 hours after treatment initiation. Although most patients do not require medical intervention, an asymptomatic second-degree Mobitz I atrioventricular block requiring medical intervention can occur in patients.

Delayed onset events including transient asystole and unexplained death, have been reported within 24 hours of the first dose. These reported cases have been confounded by concomitant medications and/or pre-existing disease. The relationship of such events to fingolimod, as contained in Filengia, is uncertain.

Blood pressure

It has been reported that fingolimod, as contained in Filengia, 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. Cases of hypertension have been reported within the first month of treatment initiation and on the first day of treatment that may require treatment with antihypertensive agents or discontinuation of fingolimod, as contained in Filengia (see also section 4.4, Blood pressure effects).

Liver function

Increased hepatic enzymes have been reported in multiple sclerosis patients treated with fingolimod, as contained in Filengia. Asymptomatic elevation in serum levels of ALT of ≥3x ULN (upper limit of normal) and ≥5x ULN has been reported. Recurrence of liver transaminase elevations has occurred upon re-challenge in some patients,

supporting a relationship to the medicine. It has been reported that 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. ALT elevations ≥5x ULN returned to normal within approximately 5 months in patients who continued treatment with fingolimod, as contained in Filengia (see section 4.4, Liver function).

Nervous system disorders

Reports have shown that rare events involving the nervous system occurred in patients treated with fingolimod, as contained in Filengia, 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 with the use of fingolimod, as contained in Filengia.

Vascular disorders

Cases of ischaemic and haemorrhagic strokes have been reported at the 0,5 mg dose. Rare cases of peripheral arterial occlusive disease were reported to have occurred in patients treated with fingolimod, as contained in Filengia, 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 fingolimod, as contained in Filengia, treatment starting at month 1 and remaining stable thereafter. At month 24, a reduction from baseline values of predicted FEV_1 has been reported. The difference resolved after treatment discontinuation.

Lymphomas

Cases of lymphoma of different varieties, including a fatal case of Epstein-Barr virus (EBV) positive B-cell lymphoma have been reported. Non-Hodgkin's lymphoma (B-cell and T-cell) cases, including cases of cutaneous T-cell lymphoma (mycosis fungoides) have been reported.

Haemophagocytic syndrome

Very rare cases of haemophagocytic syndrome (HPS) with fatal outcome have been reported in patients treated with fingolimod, as contained in Filengia, in the context of an infection. HPS is a condition that occur less frequently and has been described in association with infections, immunosuppression and a variety of autoimmune diseases.

Depression and anxiety are known to occur with increased frequency in the multiple sclerosis population. Depression and anxiety have also been reported in patients on fingolimod, as contained in Filengia.

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 to: *SAHPRA · https://www.sahpra.org.za/health-products-vigilance/*.

4.9 Overdose

Reports from clinical studies have shown that mild chest tightness or discomfort which was clinically consistent with small airway reactivity were reported in 5 of 6 healthy volunteer subjects who were administered 40 mg, (i.e. 80-fold above the recommended dose).

Filengia 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 4.3, 4.4 and 4.8).

If the overdose constitutes first exposure to Filengia 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 Filengia from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 34 Other: selective immunosuppressive agents

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

Mechanism of action

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

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

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 % Cl ≤ 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 were 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 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, Filengia 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 not be used in patients with severe hepatic impairment (Child-Pugh class C) (see section 4.3).

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

Paediatric population

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

Elderly

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised Starch NF (Starch STA-RX 1500)

Sodium Lauryl Sulphate NF (Texapon K12P)

Gelatine

Titanium dioxide

Yellow iron oxide

Printing ink

Black Iron Oxide

Potassium Hydroxide

Propylene Glycol

Shellac

Strong Ammonia Solution

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:

Aluminium – aluminium blister packs

Forming foil: Aluminium soft temper (OPA/Alum/PVC)

Lidding foil: Aluminium foil, heat sealable

Pack sizes: 7, 10, 14, 28, 30, 98 in blisters.

or

Aluminium – aluminium blister packs (peel)

Forming foil: Aluminium soft temper (OPA/Alum/PVC)

Lidding foil: Aluminium foil, peelable (Paper/PET/Alum)

Pack sizes: 10x1, 28x1, 30x1, 98x1 and 100x1 in perforated unit-dose blisters.

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

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City, Midrand

2090

8. REGISTRATION NUMBER(S)

52/34/0364

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 June 2022

10. DATE OF REVISION OF THE TEXT