PROFESSIONAL INFORMATION LEAFLET FOR MYELENEA

MYELENEA should be used only by neurologists experienced in the treatment of Multiple Sclerosis (MS).

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

6-hour monitoring (ECG, heart rate and blood pressure) on Day 1 is mandatory for all patients, in order to determine individual response to treatment initiation. Patients who experience these events or patients with risk factors (see WARNINGS AND SPECIAL PRECAUTIONS) 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

PROPRIETARY NAME AND DOSAGE FORM

MYELENEA capsules.

COMPOSITION

Each capsule contains 0,5 mg fingolimod as hydrochloride.

Inactive ingredients:

Cellulose capsule shells (containing: carrageenan, hypromellose, iron oxide yellow, potassium chloride, titanium dioxide), magnesium stearate, microcrystalline cellulose, TekPrint black ink (containing: black iron oxide, potassium hydroxide, shellac).

Sugar free.

CATEGORY AND CLASS

A 34 Other: selective immunosuppressive agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Fingolimod is a sphingosine-1-phosphate receptor modulator. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod-phosphate. Fingolimod-phosphate binds at low nanomolar concentrations to sphingosine-1-phosphate (S1P) receptors 1, 3, and 4 located on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptors 1, 3 and 5 located on neural cells in the central nervous system (CNS).

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

Effect on the immune cell numbers in the blood:

Within 4 – 6 hours after the first dose of fingolimod 0,5 mg, the lymphocyte count decreases to approximately 75 % of baseline in peripheral blood. With continued daily dosing, the lymphocyte count continues to decrease over a two-week period, reaching a nadir count of approximately 500 cells/µl or approximately 30 % of baseline. Eighteen percent of patients reached a minimal count below 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 mild decrease in the neutrophil count to approximately 80 % of baseline. Monocytes are unaffected by fingolimod.

Heart rate and rhythm:

Fingolimod causes an initial reduction in heart rate and decrease in atrioventricular conduction at treatment initiation (see **SIDE EFFECTS**). The maximal decline in heart rate is seen within 6 hours post dose (Mean -7,86; SD 8,048; Min -43,7; Median -7,67; Max 24,0), with 70 % of the negative chronotropic effect achieved on the first day. Heart rate progressively returns to baseline values within one month of chronic treatment. With initiation of fingolimod treatment there is an increase in atrial premature contractions, but there is no increased rate of atrial fibrillation/flutter or ventricular dysrhythmias or ectopy. Fingolimod treatment is not associated with a decrease in cardiac output. The decrease in heart rate induced by fingolimod can be reversed by atropine, isoprenaline or salmeterol.

Potential to prolong the QT interval:

In a QT interval study of doses of 1,25 or 2,5 mg fingolimod at steady-state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of QTcI, with the upper boundary of the 90 % confidence interval (CI) ≤ 13,0 ms. There is no dose or exposure-response relationship of fingolimod and QTcI

prolongation. There is no consistent signal of increased incidence of QTcl outliers, either absolute or change from baseline, associated with fingolimod treatment. In MS studies, there was no clinically relevant prolongation of the QT interval.

Pulmonary function:

Fingolimod treatments with single or multiple doses of 0,5 and 1,25 mg for two weeks were not associated with a detectable increase in airway resistance as measured by FEV_1 and forced expiratory flow during expiration of 25 to 75 % of the forced vital capacity (FEF_{25-75}). Single fingolimod doses ≥ 5 mg (10-fold the recommended dose) are associated with a dose-dependent increase in airway resistance. Fingolimod treatment with multiple doses of 0,5; 1,25, or 5 mg was not associated with impaired oxygenation or oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Patients on fingolimod treatment had a normal bronchodilator response to inhaled beta agonists.

Pharmacokinetic properties:

Absorption:

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

Distribution:

Fingolimod highly distributes in red blood cells, with the fraction in blood cells of 86 %. Fingolimod and fingolimod-phosphate are highly protein bound (> 99,7 %). Fingolimod and

fingolimod-phosphate protein binding is not altered by renal or hepatic impairment. Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1 200 ± 260 litres.

Metabolism:

The biotransformation of fingolimod in humans occurs by 3 main pathways: by reversible stereoselective phosphorylation to the pharmacologically active (*S*)-enantiomer of fingolimod- phosphate, by oxidative biotransformation mainly via the cytochrome P450 4F2 isoenzyme, with subsequent fatty acid-like degradation to inactive metabolites, and by formation of pharmacologically inactive non-polar ceramide analogs of fingolimod. Following single oral administration of [14C] fingolimod, the major fingolimod-related components in blood, as judged from their contribution to the AUC up to 816 hours post-dose of total radiolabelled components, are fingolimod itself (23,3 %), fingolimod-phosphate (10,3 %), and inactive metabolites (M3 carboxylic acid metabolite (8,3 %), M29 ceramide metabolite (8,9 %), and M30 ceramide metabolite (7,3 %)).

Elimination:

Fingolimod blood clearance is 6,3 ± 2,3 litre/hour, and the average apparent terminal half-life ($t_{1/2}$) is 6 to 9 days. Blood levels of fingolimod-phosphate decline in parallel with those of fingolimod in the terminal phase, yielding similar half-lives for both. After oral administration, about 81 % of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod-phosphate are not excreted intact in urine but are the major components in the faeces with amounts representing less than 2,5 % of the dose each. After 34 days, the recovery of the administered dose is 89 %.

Linearity:

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

Special populations:

Renal dysfunction:

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

Hepatic dysfunction:

The pharmacokinetics of single-dose fingolimod (1 or 5 mg), when assessed in patients with mild, moderate and severe hepatic impairments, showed no change on fingolimod C_{max}, but an increase in AUC by 12 %, 44 %, and 103 % respectively. The apparent elimination half-life of fingolimod is unchanged in mild hepatic impairment, but is prolonged by about 50 % in patients with moderate or severe hepatic impairment. Fingolimod-phosphate was measured in severe hepatic impairment only and C_{max}, and AUC were increased by 22 % and 29 %, respectively. Although hepatic impairment elicited changes in the disposition of fingolimod and fingolimod-phosphate, the magnitude of these changes suggests that the fingolimod dose does not need to be adjusted in mild or moderate hepatic impaired patients. Fingolimod should be used with caution in patients with severe hepatic impairment (Child-Pugh class C).

Paediatrics:

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

CONTRAINDICATIONS).

Elderly:

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

INDICATIONS

MYELENEA is indicated as a disease modifying therapy for the treatment of patients with relapsing Multiple Sclerosis (MS), to reduce the frequency of relapses and to delay the progression of disability.

CONTRAINDICATIONS

- Hypersensitivity to fingolimod or to any of the inactive ingredients of **MYELENEA** (see **COMPOSITION**).
- Pregnancy and lactation (see **HUMAN REPRODUCTION**).
- Concomitant administration with anti-dysrhythmic medicines; Class 1a (e.g. quinidine, procainamide), Class III (e.g. amiodarone, sotalol) (see **WARNINGS AND SPECIAL PRECAUTIONS** for risk factors).

WARNINGS AND SPECIAL PRECAUTIONS

Bradydysrhythmia:

Initiation of **MYELENEA** treatment results in a decrease in heart rate. After the first dose, the decline in heart rate starts within one hour, and is usually maximal within 6 hours, followed

by recovery and a second decrease within 24 hours. Heart rate usually normalises within one month.

With continued administration, heart rate returns towards baseline within one month of chronic treatment (see **Pharmacodynamic properties** – ***Heart rate and rhythm***). In patients receiving **MYELENEA** 0,5 mg, the decrease in heart rate, as measured by pulse, averages approximately 8 beats per minute (bpm). Heart rates below 40 bpm have been observed. Patients who experienced bradycardia were generally asymptomatic. Some patients experienced mild to moderate symptoms, including hypotension, dizziness, fatigue, palpitations and chest pain, which usually resolved within the first 24 hours on treatment.

Initiation of **MYELENEA** treatment is associated with atrioventricular conduction delays, usually as first-degree atrioventricular blocks (prolonged PR interval on electrocardiogram). Second-degree atrio-ventricular (AV) blocks, usually Mobitz type I (Wenckebach) have been observed in less than 0,5 % of patients receiving **MYELENEA** 0,5 mg. The conduction abnormalities typically, were transient, usually did not require treatment and usually resolved within the first 24-hours of treatment (see **SIDE EFFECTS**).

Cases of transient, complete AV block have been reported during post-marketing use of **MYELENEA** (see **SIDE EFFECTS**) Therefore, on initiation of **MYELENEA** treatment, it is recommended that all patients be observed, with hourly pulse and blood pressure measurement, for a period of 6 hours for signs and symptoms of bradycardia. All patients should have electrocardiogram (ECG) performed prior to dosing and at the end of the 6-hour monitoring period.

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 **MYELENEA**.

Additional observation, until the finding has resolved is also required if:

- The heart rate at 6 hours post-dose, is < 45 bpm or is the lowest value post-dose (suggesting that the maximum pharmacodynamic effect on the heart is not yet manifested).
- The ECG at 6 hours after the first dose shows new onset second degree or higher grade AV block.
- If the ECG at 6 hours shows a QTc interval ≥ 500 msec, patients should be monitored overnight.

Due to the risk of serious rhythm disturbances, **MYELENEA** should not be used in patients with second degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial heart block. Since significant bradycardia may be poorly tolerated in patients with known ischaemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, and history of recurrent syncope or severe untreated sleep apnoea, **MYELENEA** should not be used in these patients. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring, which should last overnight.

Since initiation of **MYELENEA** treatment resulted in decreased heart rate and therefore a

prolongation of the QT interval, **MYELENEA** should not be used in patients with significant QT prolongation (QTc > 470 msec (females) or > 450 msec (males)). **MYELENEA** should not be used in patients with relevant risk factors for QT prolongation (for example, hypokalaemia, hypomagnesemia, congenital QT prolongation) or in patient using medicines that prolong the QT interval. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring, which should last overnight.

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

Experience with **MYELENEA** is limited in patients receiving concurrent therapy with beta blockers, heart-rate-lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other medicines which may decrease heart rate (e.g. digoxin). Since the initiation of **MYELENEA** treatment is also associated with slowing of the heart rate, concomitant use of these medicines during **MYELENEA** initiation, may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with **MYELENEA** should not be initiated in patients who are concurrently treated with these medicines. If treatment with **MYELENEA** is considered, advice from a cardiologist should be sought regarding the switch to non heart-rate or lowering medicines appropriate monitoring for treatment initiation, which should last overnight.

If **MYELENEA** therapy is discontinued for more than 2 weeks after the first month of treatment the effects on heart rate and atrioventricular conduction may recur on reintroduction of **MYELENEA** treatment and the same precautions as for initial dosing should apply. Within the first two weeks of treatment, first dose procedures are recommended after interruption of one day or more. During week 3 and 4 of treatment, first dose procedures are recommended after treatment interruption of more than seven days.

Infections:

Before initiating treatment with **MYELENEA**, a recent complete blood count (CBC) (i.e. within 6 month or after discontinuation of prior therapy) should be available. Initiation of treatment with **MYELENEA** should be delayed in patients with severe active infection until resolution. Assessments of CBC are also recommended periodically during treatment, at month 3 and at least yearly thereafter, and in case of signs of infection.

MYELENEA causes a dose-dependent reduction in peripheral lymphocyte count to 20 % – 30 % of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues (see **PHARMACOLOGICAL ACTION**). The immune system effects of **MYELENEA** may therefore increase the risk of infections (see **SIDE EFFECTS**).

Effective diagnostic and therapeutic strategies should therefore be employed in patients with symptoms of infection while on therapy.

Because the elimination of **MYELENEA** after discontinuation may take up to 2 months, vigilance for infection should be continued throughout this period (see **Stopping therapy** below).

MYELENEA should be co-administered with caution due to the risk of additive immune system effects (see **INTERACTIONS**). Patients receiving **MYELENEA** should be instructed to report symptoms of infections to their health care provider. Suspension of dosing with **MYELENEA** should be considered if a patient develops a serious infection and consideration of benefit-risk should be undertaken prior to re-initiation of therapy.

Before initiating **MYELENEA** therapy, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody negative patients should be considered prior to commencing treatment with **MYELENEA**, following which initiation of treatment with **MYELENEA** should be postponed for 1 month to allow full effect of vaccination to occur.

Vaccination:

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

Macular oedema:

Macular oedema (see **SIDE EFFECTS**) with or without visual symptoms has been reported in 0,4 % of patients treated with **MYELENEA** 0,5 mg, occurring predominantly in the first 3 to 4 months of therapy. An ophthalmological evaluation is therefore recommended at 3 to 4 months after treatment initiation. If patients report visual disturbances at any time while on **MYELENEA** 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 **SIDE EFFECTS**). **MYELENEA** 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 **MYELENEA** in patients with macular oedema has not been evaluated. It is recommended that **MYELENEA** be discontinued if a patient develops macular oedema. A decision on whether or not **MYELENEA** 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:

Elevations of 3-fold or greater in liver transaminases occurred in 8,5 % of patients treated with **MYELENEA** 0,5 mg, and **MYELENEA** 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 **MYELENEA.** 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. **MYELENEA** should be discontinued if significant liver injury is confirmed.

Although it is not known whether patients with pre-existing liver disease are at increased risk of developing elevated liver function tests (LFTs) when taking **MYELENEA**, caution in the use of **MYELENEA** should be exercised in patients with a history of significant liver disease.

Interference with serological testing:

Since **MYELENEA** 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 **MYELENEA**. 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 medicines, were excluded from participation in premarketing clinical trials and special care is indicated if patients with uncontrolled hypertension are treated with **MYELENEA.** In MS clinical trials, patients treated with **MYELENEA** 0,5 mg had an average increase of approximately 3 mm Hg in systolic pressure, and approximately 1 mm Hg in diastolic pressure, first detected approximately 1 month after treatment initiation, and persisting with continued treatment. In the two-year placebo-controlled study, hypertension was reported as an adverse event in 6,5 % of patients on **MYELENEA** 0,5 mg and in 3,3 % of patients on placebo. Therefore, blood pressure should be regularly monitored during treatment with **MYELENEA.**

Respiratory effects:

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

Posterior reversible encephalopathy syndrome:

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported with **MYELENEA** 0,5 mg (see **SIDE EFFECTS**). 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, **MYELENEA** should be discontinued.

Co-administration with potent CYP450 inducers:

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

Cutaneous neoplasms:

Basal cell carcinoma (BCC) and other cutaneous neoplasms, including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma, have been reported in patients receiving **MYELENEA.** (see **SIDE EFFECTS**). 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 **MYELENEA** should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

Tumefactive lesions:

Cases of tumefactive lesions associated with MS relapse were reported. In case of severe relapses MRI should be performed to exclude tumefactive lesions. Discontinuation of **MYELENEA** should be considered on a case-by-case basis taking into account individual benefits and risks.

Stopping therapy:

If a decision is made to stop treatment with **MYELENEA**, the health care provider needs to be aware that **MYELENEA** remains in the blood for up to two months following the last dose. Lymphocyte counts typically return to normal range within 1 to 2 months of stopping therapy (see **Pharmacological action**). Starting other therapies during this interval will result in concomitant exposure to **MYELENEA.** Use of immunosuppressants soon after the discontinuation of **MYELENEA** may lead to an additive effect on the immune system and caution is therefore indicated.

Effects on ability to drive and use machines:

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

INTERACTIONS

Pharmacodynamic interactions:

Other anti-neoplastic, immunomodulatory or immunosuppressive therapies should be co-administered with caution, due to the risk of additive immune system effects. Caution should

also be exercised when switching patients from long-acting therapies with immune effects such as natalizumab or mitoxantrone.

When MYELENEA is used with beta blockers, there is an additional 15 % reduction of heart rate upon MYELENEA Initiation, an effect not seen with calcium channel blockers. Treatment with MYELENEA should not be initiated in patients receiving beta blockers, heart rate lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other substances which may decrease heart rate (e.g. digoxin) because of the potential additive effects on heart- rate.

If treatment with **MYELENEA** 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 **WARNINGS AND SPECIAL PRECAUTIONS**).

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

Pharmacokinetic interactions:

MYELENEA is metabolised mainly by human CYP4F2, with significant contribution also observed for CYP2D6*1, 2E1, 3A4, and 4F12. The involvement of multiple CYP isoenzymes in the oxidation of **MYELENEA** suggests that the metabolism of **MYELENEA** will not be subject to substantial inhibition in the presence of a single specific CYP inhibitor.

Potential of MYELENEA and fingolimod-phosphate to inhibit the metabolisms of co-medicine:

In vitro inhibition studies in pooled human liver microsomes and specific metabolic probe substrates demonstrated that **MYELENEA** and fingolimod-phosphate have little or no capacity to inhibit the activity of CYP450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 or CYP4A9/11). Therefore, **MYELENEA** and fingolimod-phosphate are unlikely to reduce the clearance of medicines that are mainly cleared through metabolism by the major cytochrome P450 isoenzymes.

Potential of MYELENEA and fingolimod-phosphate to induce its own and/or the metabolisms of co-medicine:

MYELENEA was examined for its potential to induce human CYP3A4, CYP1A2, CYP4F2 and ABCB1 (P-gp) mRNA and CYP3A, CYP1A2, CYP2B6, CYP2C8/9, CYP2C19 and CYP4F2 activity in primary human hepatocytes. **MYELENEA** did not induce mRNA or activity of the different CYP450 enzymes and ABCB1 with respect to the vehicle control, therefore no clinically relevant induction of the tested CYP450 enzymes or ABCB1 (P-gp) by **MYELENEA** are expected at therapeutic concentrations.

Transporters:

MYELENEA as well as fingolimod-phosphate are not expected to inhibit the uptake of co-medications and/or biologics transported by OATP1B1, OATP1B3 or NTCP. Similarly, they are not expected to inhibit the efflux of co-medicine and/or biologics transported by the resistance-associated protein 2 (MRP2) and MDR1-mediated transport at therapeutic concentrations.

Ciclosporin:

The pharmacokinetics of single-dose **MYELENEA** were not altered during co-administration with ciclosporin at steady-state, nor was ciclosporin steady-state pharmacokinetics altered by single-dose or multi-dose (28 days) **MYELENEA** administration. **MYELENEA** is unlikely to reduce the clearance of medicines mainly cleared by CYP3A4 and show that the potent inhibition of transporters PgP, MRP2 and OATP-C does not influence **MYELENEA** disposition.

Ketoconazole:

The co-administration of ketoconazole 200 mg twice daily at steady-state and a single dose of **MYELENEA** 0**,**5 mg, led to a modest Increase in the AUC of **MYELENEA** and fingolimod-phosphate (1,7-fold increase), indicating that potent inhibitors of CYP3A and CYP4F have a weak effect on **MYELENEA** pharmacokinetics.

Isoproterenol, atropine, atenolol and diltiazem:

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

Population pharmacokinetics analysis of potential medicine medicine related interactions:

A population pharmacokinetics evaluation, performed in MS patients, did not provide evidence for a significant effect of fluoxetine and paroxetine (strong CYP2D6 inhibitors) and carbamazepine (potent enzyme inducer) on fingolimod or fingolimod-phosphate

concentrations. In addition, the following, commonly prescribed medicines had no clinically relevant effect (≤ 20 %) on **MYELENEA** or fingolimod-phosphate concentrations: baclofen, gabapentin, oxybutynin, amantadine, modafinil, amitriptyline, pregabalin, corticosteroids and oral contraceptives.

Other:

Other strong CYP3A4 enzyme inducers, for example rifampicin, phenobarbitone, phenytoin, efavirenz and St. John's Wort, may reduce the AUC of **MYELENEA** and its metabolite. 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 **WARNINGS AND SPECIAL PRECAUTIONS**).

Co-administration of **MYELENEA** 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 **MYELENEA** on their exposure is not expected.

Laboratory tests:

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

HUMAN REPRODUCTION

Safety in pregnancy and lactation has not been established. **MYELENEA** should not be used in pregnancy and lactation (see **CONTRAINDICATIONS**).

Women of childbearing potential:

Before initiation of **MYELENEA** treatment, women of childbearing potential should be counselled on the potential for serious risk to the foetus and the need for effective contraception during treatment with **MYELENEA**. Since it takes approximately two months to eliminate **MYELENEA** from the body on stopping treatment (see **WARNINGS AND SPECIAL PRECAUTIONS – Stopping therapy**), the potential risk to the foetus may persist and contraception should be continued during that period.

Male reproductive toxicity:

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

DOSAGE AND DIRECTIONS FOR USE

Do not exceed the recommended dosage.

The recommended dose of **MYELENEA** is one 0,5 mg capsule taken orally once daily. **MYELENEA** 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 **MYELENEA** 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 **WARNINGS AND SPECIAL PRECAUTIONS – Bradydysrhythmia**).

Dosing in special populations:

Renal impairment:

No dose adjustments of **MYELENEA** are needed (see **Pharmacokinetic properties**).

Hepatic impairment:

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

Paediatric patients:

MYELENEA is not indicated for use in paediatric patients (see **Pharmacokinetic properties** and **CONTRAINDICATIONS**).

Elderly patients:

MYELENEA should be used with caution in patients aged 65 years and over (see **Pharmacokinetic properties**).

Diabetic patients:

MYELENEA should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular oedema (see **WARNINGS AND SPECIAL PRECAUTIONS).**

SIDE EFFECTS

Infections and infestations

Frequent: Influenza viral infections, bronchitis, sinusitis, gastroenteritis, herpes viral infections, tinea infections.

Less frequent: Pneumonia.

Frequency unknown: Cryptococcal infections, progressive multifocal leukoencephalopathy.

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

Frequent: Basal cell carcinoma.

Less frequent: Malignant melanoma, lymphoma, squamous cell carcinoma, Kaposi's carcinoma.

Frequency unknown: Merkel cell carcinoma.

Blood and the lymphatic system disorders

Frequent: Leucopenia, lymphopenia.

Less frequent: Thrombocytopenia.

Frequency unknown: Peripheral oedema.

Immune system disorders

Frequency unknown: Hypersensitivity, rash.

Psychiatric disorders

Frequent:	Depression.
Less frequent:	Depressed mood.

Nervous system disorders

Frequent:	Headache, dizziness, paraesthesia, migraine.
Less frequent:	Posterior reversible encephalopathy syndrome (PRES), seizure.

Eye disorders

Frequent:	Eye pain, blurred vision.
Less frequent:	Macular oedema.

Cardiac disorders

Frequent:	Bradycardia, atrioventricular (AV) block.
Less Frequent:	T-wave inversion.

Vascular disorders

Frequent:	Hypertension.
Less frequent:	Peripheral arterial occlusive disease.

Respiratory, thoracic and mediastinal disorders

Frequent:	Cough, dyspnoea.

Gastrointestinal disorders

Frequent:	Diarrhoea.
Less frequent:	Nausea.

Skin and subcutaneous tissue disorders

Frequent:	Eczema, alopecia, pruritus.

Musculoskeletal, connective tissue and bone disorders

Frequent:	Back pain, myalgia, arthralgia.

General disorders and administrative site conditions

Frequent:	Asthenia.

Investigations

Frequent:	Increased alanine transaminase (ALT), gamma- glutamyl transferase (GGT), hepatic enzyme and blood triglycerides; weight decreased; abnormal liver function test.

Less frequent: Neutrophil count decreased.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

No cases of overdosage have been reported. However, single doses up to 80-fold the recommended dose (0,5 mg) were well tolerated in healthy volunteers. At 40 mg, 5 of 6 subjects reported mild chest tightness or discomfort which was clinically consistent with small airway reactivity.

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

IDENTIFICATION

Yellow opaque cap / white opaque body, size 3 capsule, imprinted with “A190” on cap in black ink and filled with white to off-white powder.

PRESENTATION

Three ply, cold formable silver aluminium plastic / silver push through primer foil, containing 10 capsules each, stored in an outer carton.

Pack size: 30 capsules.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from moisture.

Keep blister strips in outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

50/34/0830

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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