

NEW ZEALAND DATA SHEET

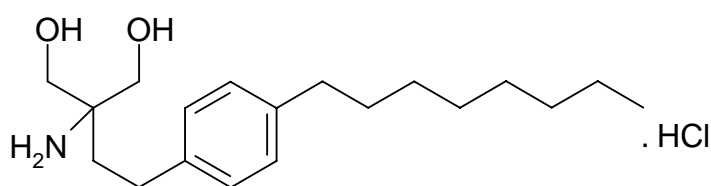
GILENYA[®]
Fingolimod

NAME OF THE MEDICINE

The active ingredient of GILENYA is fingolimod.

Chemical name: 2-amino-2-(2-(4-octylphenyl)ethyl]propan-1,3-diol hydrochloride

Chemical structure:



Molecular formula: C₁₉H₃₃NO₂ · HCl

CAS number: 162359-56-0

Molecular weight: 343.93

DESCRIPTION

Fingolimod hydrochloride is a white to almost white crystalline powder which is freely soluble in water.

Each GILENYA capsule contains 0.5 mg fingolimod, mannitol, magnesium stearate, titanium dioxide and gelatin.

PHARMACOLOGY

Mechanism of action

Fingolimod is a sphingosine-1-phosphate receptor modulator. Fingolimod is metabolized 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 pathogenic lymphocyte 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.

Pharmacodynamics

Immune system

Effects on 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. With continued daily dosing, the lymphocyte count continues to decrease over a two week period, reaching a nadir count of approximately 500 cells/ μ L or approximately 30% of baseline. Eighteen percent of patients reached a nadir of < 200 cells/ μ L on at least one occasion. Low lymphocyte counts are maintained with chronic daily dosing. The majority of T and B lymphocytes regularly traffic through lymphoid organs and these are the cells mainly affected by fingolimod. Approximately 15-20% of T lymphocytes have an effector memory phenotype, cells that are important for peripheral immune surveillance. Since this lymphocyte subset typically does not traffic to lymphoid organs it is not affected by fingolimod. 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 a transient reduction in heart rate and atrio-ventricular conduction at treatment initiation (see **PRECAUTIONS; Bradyarrhythmia and ADVERSE REACTIONS**). The maximal decline of heart rate is seen in the first 4-5 hours post dose, 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.

Autonomic responses of the heart, including diurnal variation of heart rate and response to exercise are not affected by fingolimod 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 arrhythmias 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 thorough 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 bound of the 90% 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 QTcI outliers, either absolute or change from baseline, associated with fingolimod treatment. In the multiple sclerosis studies, there was no clinically relevant prolongation of 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 forced expiratory volume in 1 second (FEV₁) and forced expiratory flow during expiration of 25 to 75% of the forced vital capacity (FEF₂₅₋₇₅). However, single fingolimod doses ≥ 5 mg (10-fold the recommended dose) are associated with a dose-dependent increase in airway resistance. Fingolimod treatment with multiple doses of 0.5, 1.25, or 5 mg is not associated with impaired oxygenation or oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Subjects on fingolimod treatment have a normal bronchodilator response to inhaled β -agonists

Pharmacokinetics

Absorption:

Fingolimod absorption is slow (t_{\max} of 12-16 hours) and extensive ($\geq 85\%$, 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. Therefore GILENYA may be taken without regard to meals (see **DOSAGE AND ADMINISTRATION**).

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-phosphate has a smaller uptake in blood cells of $< 17\%$. Fingolimod and fingolimod-phosphate are highly protein bound ($> 99.7\%$). Fingolimod and fingolimod-phosphate protein binding is not altered by renal or hepatic impairment.

Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1200 ± 260 L.

Metabolism:

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 mainly via the cytochrome P450 4F2 isoenzyme 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 [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 radiolabeled 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-phosphate decline in parallel with fingolimod in the terminal phase yielding similar half-lives for both.

After an oral administration, about 81% of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod-phosphate are not excreted intact in urine but are the major components in the faeces with amounts representing less than 2.5% of the dose each. After 34 days, the recovery of the administered dose is 89%.

Linearity

Fingolimod and fingolimod-phosphate concentrations increase in an apparent dose proportional manner after multiple once daily doses of fingolimod 0.5 mg or 1.25 mg.

Pharmacokinetics in special patient groups

Pharmacokinetics in children:

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

Pharmacokinetics in the 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.

Pharmacokinetics in patients with impaired renal or hepatic function:

Severe renal impairment increases fingolimod C_{max} and AUC by 32% and 43%, respectively, and fingolimod-phosphate C_{max} and AUC by 25% and 14%, respectively. The apparent elimination half-life is unchanged for both analytes. No GILENYA dose adjustments are needed in patients with renal impairment.

The pharmacokinetics of single-dose fingolimod (1 or 5 mg), when assessed in subjects 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

is unchanged in mild hepatic impairment but is prolonged by 49-50% in moderate and severe hepatic impairment. Fingolimod-phosphate was measured in severe hepatic impairment only, and C_{max} and AUC were decreased 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).

Ethnicity:

The effects of ethnic origin on fingolimod and fingolimod phosphate pharmacokinetics are not of clinical relevance.

Gender:

Gender has no influence on fingolimod and fingolimod-phosphate pharmacokinetics.

CLINICAL TRIALS

The efficacy of GILENYA has been demonstrated in two studies which evaluated once daily doses of GILENYA 0.5 mg and 1.25 mg in patients with relapsing remitting multiple sclerosis. Both studies included patients who had experienced at least 2 clinical relapses during the 2 years prior to randomization or at least 1 clinical relapse during the 1 year prior to randomization, and had an Expanded Disability Status Scale (EDSS) between 0 to 5.5.

Study D2301 (FREEDOMS) was a 2-year randomized, double-blind, placebo-controlled Phase III study in patients with relapsing-remitting multiple sclerosis who had not received any interferon-beta or glatiramer acetate for at least the previous 3 months and had not received any natalizumab for at least the previous 6 months. Neurological evaluations were performed at Screening, every 3 months and at time of suspected relapse. MRI evaluations were performed at Screening, month 6, month 12 and month 24. The primary endpoint was the annualized relapse rate.

Median age was 37 years, median disease duration was 6.7 years and median EDSS score at baseline was 2.0. Patients were randomized to receive GILENYA 0.5 mg (n=425) or GILENYA 1.25 mg (n=429), or placebo (n=418) for up to 24 months. Median time on study drug was 717 days on 0.5 mg, 715 days on 1.25 mg and 718.5 days on placebo.

The annualized relapse rate was significantly lower in patients treated with GILENYA than in patients who received placebo. The key secondary endpoint was the time to 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5 point increase for patients with baseline EDSS of 5.5) sustained for 3 months. Time to onset of 3-month confirmed disability progression was significantly delayed with GILENYA treatment compared to placebo. There were no significant differences between the 0.5 mg and the 1.25 mg doses on either endpoint.

The results for this study are shown in Table 1 and Figures 1 and 2

Table 1 Clinical and MRI results of Study D2301

	GILENYA 0.5 mg	GILENYA 1.25 mg	Placebo
Clinical Endpoints	N=425	N=429	N=418
Annualized relapse rate (primary endpoint)	0.18 (p<0.001*)	0.16 (p<0.001*)	0.40
Relative reduction (percentage)	54	60	
Percent of patients remaining relapse-free at 24 months	70.4 (p<0.001*)	74.7 (p<0.001*)	45.6
Risk of disability progression			
Hazard ratio (95% CI) (3-month confirmed)	0.70 (0.52, 0.96) (p=0.024*)	0.68 (0.50, 0.93) (p=0.017*)	
Hazard ratio (95% CI) (6-month confirmed)	0.63 (0.44, 0.90) (p=0.012*)	0.60 (0.41, 0.86) (p=0.006*)	
MRI Endpoints			
Number of new or newly enlarging T2 lesions	n=370	n=337	n=339
Median (mean) number over 24 months	0.0 (2.5) (p<0.001*)	0.0 (2.5) (p<0.001*)	5.0 (9.8)
Number of Gd-enhancing lesions	n=369 (Month 24)	n=343 (Month 24)	n=332 (Month 24)
Median (mean) number at			
Month 6	0.0 (0.2)	0.0 (0.3)	0.0 (1.3)
Month 12	0.0 (0.2)	0.0 (0.3)	0.0 (1.1)
Month 24	0.0 (0.2) (p<0.001* at each timepoint)	0.0 (0.2) (p<0.001* at each timepoint)	0.0 (1.1)
Percent change in T2 lesion total volume	n=368	n= 343	n=339
Median (mean) % change over 24 months	-1.7 (10.6) (p<0.001*)	-3.1 (1.6) (p<0.001*)	8.6 (33.8)
Change in T1 hypointense lesion volume	n=346	n=317	n=305
Median (mean) % change over 24 months	0.0 (8.8) (p=0.012*)	-0.2 (12.2) (p=0.015*)	1.6 (50.7.)
Percent change in brain volume	n=357	n=334	n=331
Median (mean) % change over 24 months	-0.7 (-0.8) (p<0.001*)	-0.7 (-0.9) (p<0.001*)	-1.0 (-1.3)

All analyses of clinical endpoints were intent-to treat. MRI analyses used evaluable dataset.

* Indicates statistical significance vs. placebo at two-sided 0.05 level.

Determination of p-values: aggregate ARR by negative binomial regression adjusting for treatment, pooled country, number of relapses in previous 2 years and baseline EDSS; percent of patients maintaining relapse-free logistic regression adjusted for treatment, country, number of relapse in previous 2 years, and baseline EDSS; time to 3-month/6-month confirmed disability progression by Cox's proportional hazards model adjusted for treatment, pooled country, baseline EDSS, and age; new/newly enlarging T2 lesions by negative binomial regression adjusted for treatment and pooled country; Gd-enhancing lesions by rank ANCOVA adjusted for treatment, pooled country, and baseline number of Gd-enhancing lesions; and % change in lesion and brain volume by rank ANCOVA adjusted for treatment, pooled country, and corresponding baseline value.

Figure 1 Kaplan-Meier plot for time to first confirmed relapse up to Month 24– Study D2301 (ITT population)

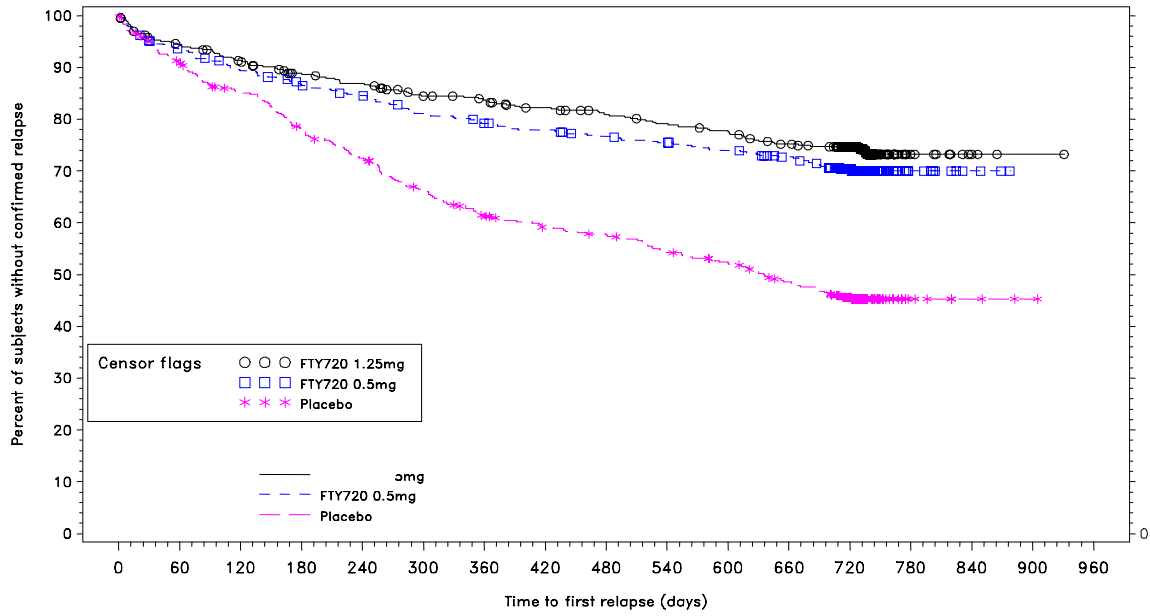
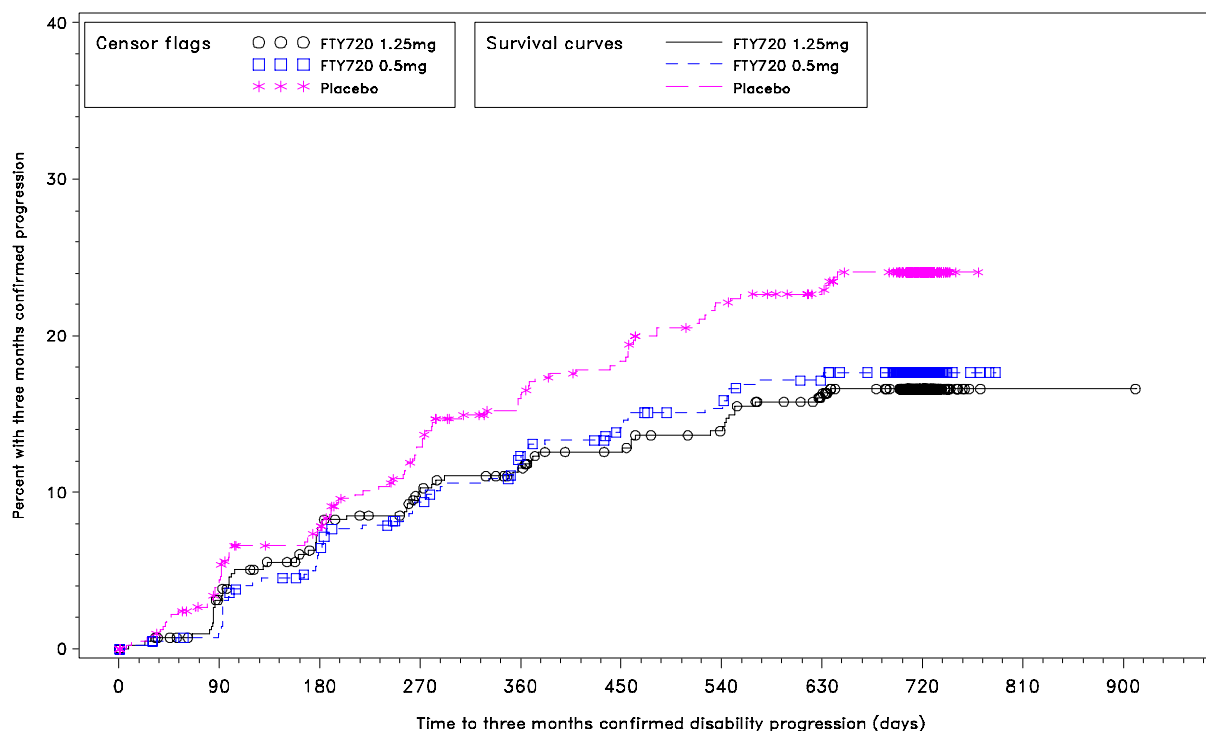


Figure 2 Cumulative plot of time to 3-month confirmed disability progression – Study D2301 (ITT population)



Study D2302 (TRANSFORMS) was a 1-year randomized, double-blind, double-dummy, active (interferon beta-1a 30 micrograms, intramuscular, once weekly)-controlled Phase III study in patients with RRMS who had not received any natalizumab in the previous 6 months. Prior therapy with interferon-beta or glatiramer acetate up to the time of randomization was permitted.

Neurological evaluations were performed at Screening, every 3 months and at the time of suspected relapses. MRI evaluations were performed at Screening and at month 12. The primary endpoint was the annualized relapse rate.

Median age was 36 years, median disease duration was 5.9 years and median EDSS score at baseline was 2.0. Patients were randomized to receive GILENYA 0.5 mg (n=431) or 1.25 mg (n=426) or interferon beta-1a 30 micrograms via the intramuscular route once weekly (n=435) for up to 12 months. Median time on study drug was 365 days on 0.5 mg, 354 days on 1.25 mg and 361 days on interferon beta-1a IM.

The annualized relapse rate was significantly lower in patients treated with GILENYA than in patients who received interferon beta-1a IM. There was no significant difference between the GILENYA 0.5 mg and the 1.25 mg doses. The key secondary endpoints were number of new or newly enlarging T2 lesions and time to onset of 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5 point increase for those with baseline EDSS of 5.5) sustained for 3 months. The number of new or newly enlarging T2 lesions was significantly lower in patients treated with GILENYA than in

patients who received interferon beta-1a IM. There was no significant difference in the time to 3-month confirmed disability progression between GILENYA and interferon beta-1a-treated patients at 1 year. There were no significant differences between the 0.5 mg and the 1.25 mg doses on either endpoint.

The results for this study are shown in Table 2 and Figure 3.

Table 2 Clinical and MRI results of Study D2302

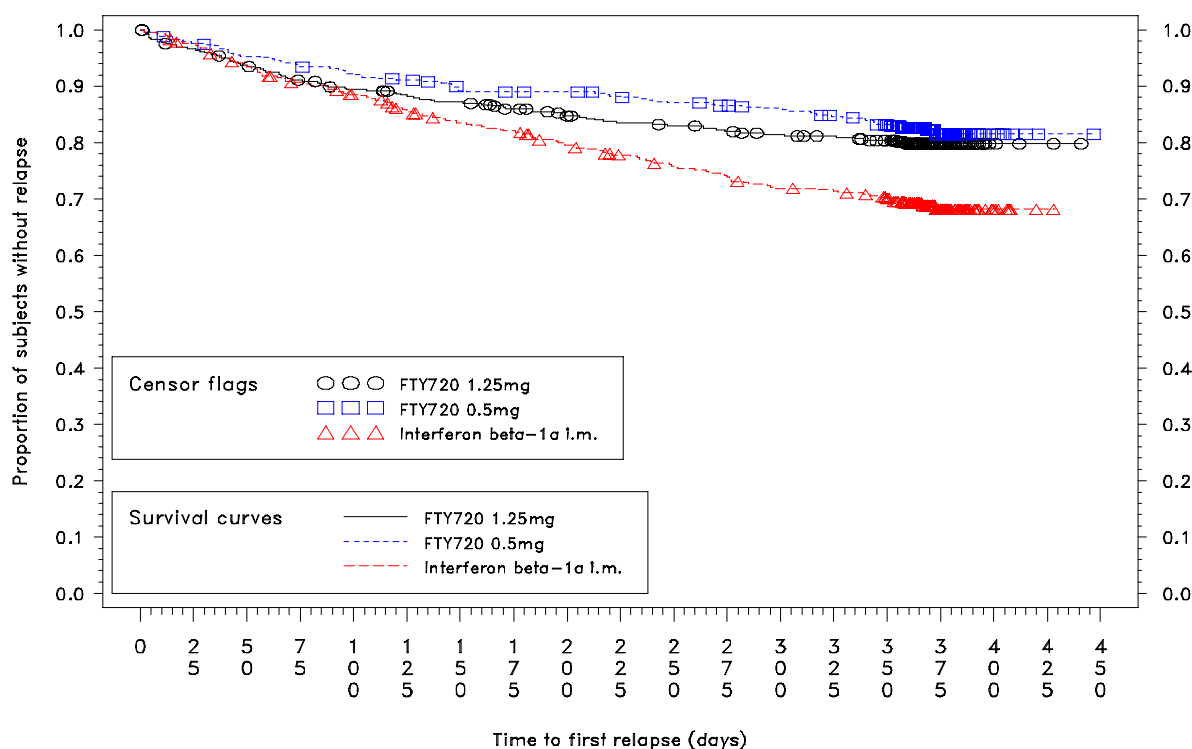
	GILENYA 0.5 mg	GILENYA 1.25 mg	Interferon beta-1a, IM 30µg,
Clinical Endpoints	N=429	N=420	N=431
Annualized relapse rate (primary endpoint)	0.16 (p<0.001*)	0.20 (p<0.001*)	0.33
Relative reduction (percent)	52	38	
Percent of patients remaining relapse-free at 12 months	82.5 (p<0.001*)	80.5 (p<0.001*)	70.1
Risk of disability progression			
Hazard ratio (95% CI) (3-month confirmed)	0.71 (0.42, 1.21) (p=0.209)	0.85 (0.51, 1.42) (p=0.543)	
MRI Endpoints			
Number of new or newly enlarging T2 lesions	n=380	n=356	n=365
Median (mean) number over 12 months	0.0 (1.7) (p=0.004*)	1.0 (1.5) (p<0.001*)	1.0 (2.6)
Number of Gd-enhancing lesions	n=374	n=352	n=354
Median (mean) number at 12 months	0.0 (0.2) (p<0.001*)	0.0 (0.1) (p<0.001*)	0.0 (0.5)
Percent change in brain volume	n=368	n=345	n=359
Median (mean) % change over 12 months	-0.2 (-0.3) (p<0.001*)	-0.2 (-0.3) (p<0.001*)	-0.4 (-0.5)

All analyses of clinical endpoints were intent-to treat. MRI analyses used evaluable dataset.

* Indicates statistical significance vs. Interferon beta-1a IM at two-sided 0.05 level.

Determination of p-values: aggregate ARR by negative binomial regression adjusting for treatment, country, number of relapses in previous 2 years and baseline EDSS; percent of patients maintaining relapse-free logistic regression adjusted for treatment, country, number of relapse in previous 2 years, and baseline EDSS; risk of disability progression by Cox's proportional hazards model adjusted for treatment, country, baseline EDSS, and age; new/newly enlarging T2 lesions by negative binomial regression adjusted for treatment, country, number of relapses in previous 2 years and baseline EDSS; Gd-enhancing lesions by rank ANCOVA adjusted for treatment, country, and baseline number of Gd-enhancing lesions; and % change in brain volume by Wilcoxon rank sum test.

Figure 3 Kaplan-Meier plot for time to first confirmed relapse up to Month 12 – Study D2302 (ITT population)



Pooled results of studies D2301 and D2302 showed a consistent reduction of annualized relapse rate compared to comparator in subgroups defined by gender, age, prior multiple sclerosis therapy, disease activity or disability levels at baseline.

INDICATIONS

GILENYA 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.

CONTRAINDICATIONS

GILENYA should not be administered to patients with known hypersensitivity to fingolimod or any of the excipients.

PRECAUTIONS

Infections

A core pharmacodynamic effect of GILENYA is a dose dependent reduction of peripheral lymphocyte count to 20 - 30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues (see **PHARMACOLOGY**).

The immune system effects (see **PHARMACOLOGY**) of GILENYA may increase the risk of infections (see **ADVERSE REACTIONS**). Effective diagnostic and therapeutic strategies should therefore be employed in patients with symptoms of infection while on therapy. Because the elimination of fingolimod after discontinuation may take up to two months, vigilance for infection should be continued throughout this period (see **Stopping GILENYA therapy**).

Anti-neoplastic, immunosuppressive or immune modulating therapies should be co-administered with caution due to the risk of additive immune system effects (see **Interactions with other drugs**).

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

As could be considered for any immune modulating drug, before initiating GILENYA 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 GILENYA, following which initiation of treatment with GILENYA 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 GILENYA (see **Stopping GILENYA therapy**). The use of live attenuated vaccines should be avoided.

Macular Oedema

Macular oedema (see **ADVERSE REACTIONS**) with or without visual symptoms has been reported in 0.4% of patients treated with GILENYA 0.5 mg, occurring predominantly in the first 3-4 months of therapy. An ophthalmologic evaluation is therefore recommended at 3-4 months after treatment initiation. If patients report visual disturbances at any time while on GILENYA 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 **ADVERSE REACTIONS**). GILENYA 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 ophthalmologic evaluation prior to initiating GILENYA therapy and have follow-up evaluations while receiving GILENYA therapy.

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

Bradycardia

Initiation of GILENYA treatment results in a transient decrease in heart rate. After the first dose, the heart rate decrease starts within an hour and the Day 1 decline is maximal at approximately 4-5 hours. Therefore on initiation of Gilenya treatment, it is recommended that all patients be observed for a period of 6 hours for signs and symptoms of bradycardia.

With continued dosing, heart rate returns to baseline within one month of chronic treatment (see **PHARMACOLOGY, Heart rate and rhythm**). In patients receiving GILENYA 0.5 mg this decrease in heart rate, as measured by pulse, averages approximately 8 beats per minute (bpm). Heart rates below 40 bpm were rarely observed (see **ADVERSE REACTIONS**). Patients who experienced bradycardia were generally asymptomatic but some patients experienced mild to moderate symptoms, including dizziness, fatigue, palpitations, which resolved within the first 24 hours on treatment.

Initiation of GILENYA treatment has been associated with atrio-ventricular conduction delays, usually as first-degree atrio-ventricular blocks (prolonged PR interval on electrocardiogram). Second-degree atrio-ventricular blocks, usually Mobitz type I (Wenckebach) have been observed in less than 0.5% of patients receiving GILENYA 0.5 mg in clinical trials. The conduction abnormalities typically were transient, asymptomatic, usually did not require treatment and resolved within the first 24-hours on treatment (see **ADVERSE REACTIONS**).

GILENYA has not been studied in patients with sitting heart rate less than 55 bpm, in those receiving concurrent therapy with beta blockers or in those with a history of syncope.

Gilenya has also not been studied in patients with 2nd-degree or higher AV blocks, sick-sinus-syndrome, ischemic cardiac disease, or congestive heart failure. Use of Gilenya in such patients should be based on overall benefit-risk assessment and careful observation during initiation of therapy is recommended due to potential for serious rhythm disturbances.

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

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

If GILENYA therapy is discontinued for more than 2 weeks the effects on heart rate and atrio-ventricular conduction may recur on reintroduction of GILENYA treatment and the same precautions as for initial dosing should apply.

Liver function

During clinical trials, 3-fold or greater elevation in liver transaminases occurred in 8.5% of patients treated with GILENYA 0.5 mg and drug was discontinued if the elevation exceeded 5-fold increase. Recurrence of liver transaminase elevations occurred upon re-challenge in some patients, supporting a relationship to the drug. 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 GILENYA should be discontinued if significant liver injury is confirmed (see **ADVERSE REACTIONS, Liver Transaminase**). Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function tests (LFTs) when taking GILENYA, caution in the use of GILENYA should be exercised in patients with a history of significant liver disease.

Stopping therapy

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

Effects on fertility

Data from preclinical studies does not suggest that fingolimod would be associated with an increased risk of reduced fertility.

Male reproductive toxicity

Available data do not suggest that GILENYA would be associated with an increased risk of male-mediated fetal toxicity.

Use in Pregnancy (Category D)

The use of GILENYA in women who are or may become pregnant should only be considered if the potential benefit justifies the potential risk to fetus (see **Women of childbearing potential**).

Animal studies have shown reproductive toxicity including fetal loss and organ defects, notably persistent truncus arteriosus and ventricular septal defect. Furthermore, the receptor affected by fingolimod (sphingosine-1-phosphate receptor) is known to be involved in vascular formation during embryogenesis. At the present time it is not known whether cardiovascular malformations will be found in humans. There are very limited data from the use of fingolimod in pregnant women. In clinical trials, 20 pregnancies were reported in

patients exposed to fingolimod at the time of diagnosis of pregnancy, but data are too limited to draw conclusions on safety of GILENYA in pregnancy

Fingolimod and its metabolites crossed the placental barrier in pregnant rabbits.

Fingolimod was teratogenic in the rat when given at doses of 0.1 mg/kg or higher. The most common fetal visceral malformations included persistent truncus arteriosus and ventricular septum defect. An increase in post-implantation loss was observed in rats at 1 mg/kg and higher and a decrease in viable fetuses at 3 mg/kg. Fingolimod was not teratogenic in the rabbit, where an increased embryo-fetal mortality was seen at doses of 1.5 mg/kg and higher, and a decrease in viable fetuses as well as fetal growth retardation at 5 mg/kg.

In rats, F1 generation pup survival was decreased in the early postpartum period at doses that did not cause maternal toxicity. However, F1 body weights, development, behavior, and fertility were not affected by treatment with fingolimod. In a toxicity study in juvenile rats, no additional target organs of toxicity were observed compared to adult rats. Repeated stimulations with Keyhole Limpet Hemocyanin (KLH) showed a moderately decreased response during the treatment period, but fully functional immune reactions at the end of an 8 week recovery period

Use in Lactation

Fingolimod is excreted in milk of treated animals during lactation. Because of the potential for serious adverse drug reactions in nursing infants from fingolimod, women receiving GILENYA should not breast feed.

Labour and delivery

There are no data on the effects of fingolimod on labor and delivery.

Women of childbearing potential

Before initiation of GILENYA treatment, women of childbearing potential should be counselled on the potential for serious risk to the fetus and the need for effective contraception during treatment with GILENYA. Since it will take approximately 2 months to eliminate the compound from the body upon stopping treatment (see **PRECAUTIONS**) risk potential to the fetus may persist and contraception should be pursued during that period.

General toxicity

The preclinical safety profile of fingolimod was assessed in mice, rats, dogs and monkeys. The major target organs were the lymphoid system (lymphopenia and lymphoid atrophy), lungs (increased weight, smooth muscle hypertrophy at the bronchio-alveolar junction), and heart (negative chronotropic effect, increase in blood pressure, perivascular changes and myocardial degeneration) in several species; blood vessels (vasculopathy) in rats only; and pituitary, forestomach, liver, adrenals, gastrointestinal tract and nervous system at high doses only (often associated with signs of general toxicity) in several species

Carcinogenicity

No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of fingolimod up to the maximally tolerated dose of 2.5 mg/kg, representing an approximate 50-fold margin based on the human systemic exposure (AUC) at the 0.5 mg dose. However, in a 2-year mouse study, an increased incidence of malignant lymphoma was seen at doses of 0.25 mg/kg and higher, representing an approximate 6-fold margin based on the human systemic exposure (AUC) at a daily dose of 0.5 mg

Mutagenicity

Fingolimod was not mutagenic in an Ames test and in a L5178Y mouse lymphoma cell line *in vitro*. No clastogenic effects were seen *in vitro* in V79 Chinese hamster lung cells. Fingolimod-induced numerical (polyploidy) chromosomal aberrations in V79 cells at concentrations of 3.7 µg/mL and above. Fingolimod was not clastogenic in the *in vivo* micronucleus tests in mice and rats.

Interactions with Other Drugs

Pharmacodynamic interactions

Anti-neoplastic, immunosuppressive or immune modulating therapies should be co-administered with caution due to the risk of additive immune system effects. Caution should also be applied when switching patients from long-acting therapies with immune effects such as natalizumab or mitoxantrone. In multiple sclerosis clinical trials the concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection.

Fingolimod treatment can be used in combination with heart rate lowering drugs such as atenolol and diltiazem. When fingolimod is used with atenolol, there is an additional 15% reduction of heart rate upon fingolimod initiation, an effect not seen with diltiazem. At treatment initiation in patients receiving beta blockers caution should be exercised because of the additive effects on heart rate.

During and for up to two months after treatment with GILENYA vaccination may be less effective. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided (see **ADVERSE REACTIONS**).

Pharmacokinetic interactions

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

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

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

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

Fingolimod was examined for its potential to induce human CYP3A4, CYP1A2, CYP4F2, and MDR1 (P-glycoprotein) mRNA and CYP3A, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP4F2 activity in primary human hepatocytes. Fingolimod did not induce mRNA or activity of the different CYP450 enzymes and MDR1 with respect to the vehicle control therefore no clinically relevant induction of the tested CYP450 enzymes or MDR1 by fingolimod are expected at therapeutic concentrations.

Transporters

Fingolimod 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-medications and/or biologics transported by the breast cancer resistant protein (MXR), the bile salt export pump (BSEP), the multidrug resistance-associated protein 2 (MRP2) and MDR1-mediated transport at therapeutic concentrations.

Cyclosporine

The pharmacokinetics of single-dose fingolimod were not altered during co-administration with cyclosporine at steady-state, nor was cyclosporine steady-state pharmacokinetics altered by single-dose, or multi-dose (28 days) fingolimod administration. These data indicate that fingolimod is unlikely to reduce the clearance of drugs mainly cleared by CYP3A4 and show that the potent inhibition of transporters MDR1, MRP2 and OATP-C does not influence fingolimod disposition.

Ketoconazole

The co-administration of oral ketoconazole 200 mg twice daily at steady-state and a single dose of fingolimod 5 mg led to a modest increase in the AUC of fingolimod and fingolimod-phosphate (1.7-fold increase), indicating that potent inhibitors of CYP3A and CYP4F have a weak effect on fingolimod pharmacokinetics.

Isoproterenol, atropine, atenolol, and diltiazem

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

Population pharmacokinetics analysis of potential drug-drug interactions

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

Laboratory tests

Since fingolimod reduces blood lymphocyte counts via re-distribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilized to evaluate the lymphocyte subset status of a patient treated with GILENYA.

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

ADVERSE REACTIONS

A total of 1703 patients on GILENYA (0.5 or 1.25 mg dose) constituted the safety population in the two Phase III studies in patients with relapsing remitting multiple sclerosis (see **CLINICAL TRIALS**). Study D2301 (FREEDOMS) was a 2-year placebo-controlled clinical study in 854 multiple sclerosis patients treated with fingolimod (placebo: 418). In this study the most serious adverse reactions (ADRs) for the 0.5 mg recommended therapeutic dose were infections, macular oedema and transient atrio-ventricular blocks on treatment initiation. The most frequent ADRs (incidence $\geq 10\%$) at the 0.5 mg dose were headache, influenza, diarrhoea, back pain, liver enzyme elevations and cough. The most frequent adverse event reported for GILENYA 0.5 mg at an incidence greater than 1% leading to treatment interruption included serum transaminase elevations (3.8%).

The ADRs in Study D2302 (TRANSFORMS), a 1-year controlled study using interferon beta-1a as comparator in 849 patients with multiple sclerosis treated with fingolimod), were generally similar to Study D2301, taking into account the differences in study duration.

ADRs are listed according to MedDRA system organ class. Frequencies were defined as follows: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 3 ADRs occurring in $\geq 1\%$ of patients in Study D2301, and reported for GILENYA 0.5 mg at $\geq 1\%$ higher rate than for placebo

Primary system organ class Preferred Term	Placebo N=418 %	Fingolimod 0.5mg N=425 %	Fingolimod 1.25mg N=429 %	Frequency range for the 0.5 mg dose
Infections				
Influenza viral infections	41 (9.8)	55 (12.9)	40 (9.3)	very common
Bronchitis	15 (3.6)	34 (8.0)	39 (9.1)	common
Sinusitis	19 (4.5)	28 (6.6)	27 (6.3)	common
Gastroenteritis	13 (3.1)	19 (4.5)	18 (4.2)	common
Pneumonia*	1 (0.2)	2 (0.5)	7 (1.6)	uncommon
Herpes viral infections*	33 (7.9)	37 (8.7)	25 (5.8)	common
Tinea infections	6 (1.4)	16 (3.8)	6 (1.4)	common
Cardiac Disorders				
Bradycardia	4 (1.0)	15 (3.5)	10 (2.3)	common
Nervous system disorders				
Headache	96 (23.0)	107 (25.2)	114 (26.6)	very common
Dizziness	23 (5.5)	31 (7.3)	30 (7.0)	common
Paraesthesia	18 (4.3)	23 (5.4)	17 (4.0)	common
Migraine	6 (1.4)	20 (4.7)	15 (3.5)	common
Gastrointestinal disorders				
Diarrhoea	31 (7.4)	50 (11.8)	40 (9.3)	very common
General disorders and administration site conditions				
Asthenia	5 (1.2)	11 (2.6)	9 (2.1)	common
Musculoskeletal and connective tissue disorders				
Back pain	29 (6.9)	50 (11.8)	45 (10.5)	very common
Skin and subcutaneous tissue disorders				
Eczema	8 (1.9)	14 (3.3)	15 (3.5)	common
Alopecia	10 (2.4)	15 (3.5)	9 (2.1)	common
Pruritus	5 (1.2)	11 (2.6)	4 (0.9)	common
Investigations				
Alanine transaminase (ALT) increased	16 (3.8)	43 (10.1)	50 (11.7)	very common
Gamma-glutamyl transferase (GGT) increased	4 (1.0)	22 (5.2)	32 (7.5)	common
Hepatic enzyme increased	1 (0.2)	14 (3.3)	22 (5.1)	common
Weight decreased	14 (3.3)	20 (4.7)	15 (3.5)	common

Primary system organ class Preferred Term	Placebo N=418 %	Fingolimod 0.5mg N=425 %	Fingolimod 1.25mg N=429 %	Frequency range for the 0.5 mg dose
Blood triglycerides increased	5 (1.2)	11 (2.6)	8 (1.9)	common
Liver function test abnormal	1 (0.2)	6 (1.4)	7 (1.6)	common
Respiratory, thoracic and mediastinal disorders				
Cough	34 (8.1)	43 (10.1)	37 (8.6)	very common
Dyspnoea	19 (4.5)	34 (8.0)	28 (6.5)	common
Psychiatric disorders				
Depression	28 (6.7)	33 (7.8)	26 (6.1)	common
Eye disorders				
Eye pain	6 (1.4)	11 (2.6)	8 (1.9)	common
Vision blurred	6 (1.4)	15 (3.5)	8 (1.9)	common
Macular oedema	0 (0.0)	0 (0.0)	7 (1.6)	uncommon*†
Vascular disorders				
Hypertension	16 (3.8)	27 (6.4)	28 (6.5)	common
Blood and lymphatic system disorders				
Leucopenia	1 (0.2)	12 (2.8)	27 (6.3)	common
Lymphopenia	2 (0.5)	15 (3.5)	23 (5.4)	common

* Plausible relationship to study drug

†Not reported in Study D2301 at the 0.5 mg dose; however cases were reported in other studies at that dose. Frequency category is based on the incidence at the 0.5 mg dose in Study D2302

Infections

In multiple sclerosis clinical trials, the overall rate of infections (72%) and serious infections (2%) at the 0.5 mg dose was similar to placebo. However, lower respiratory tract infections, bronchitis and pneumonia, were more common in GILENYA treated patients.

Two serious cases of disseminated herpes infection which were fatal have occurred on the 1.25 mg dose; a case of herpes encephalitis in a patient in whom initiation of acyclovir therapy was delayed by one week and a case of a primary disseminated varicella zoster infection in a patient not previously exposed to varicella receiving concomitant high-dose steroid therapy for a multiple sclerosis relapse.

Macular Oedema

In clinical trials, macular oedema occurred in 0.4% of patients treated with the recommended GILENYA dose of 0.5 mg and in 1.1% of patients treated with the higher 1.25 mg dose.

The majority of cases in multiple sclerosis clinical trials occurred within the first 3-4 months of therapy. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmologic examination. The macular oedema generally improved or resolved spontaneously after drug discontinuation. The risk of recurrence after re-challenge has not been evaluated.

Macular oedema incidence is increased in multiple sclerosis patients with a history of uveitis (approximately 20% with a history of uveitis vs 0.6% without a history of uveitis).

GILENYA has not been tested in multiple sclerosis patients with diabetes mellitus. In renal transplant clinical studies where patients with diabetes mellitus were included, therapy with GILENYA 2.5 mg and 5 mg resulted in a 2-fold increase in the incidence of macular oedema. Multiple sclerosis patients with diabetes mellitus are therefore expected to be at a higher risk for macular oedema (see **PRECAUTIONS**).

Bradycardia

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

In multiple sclerosis clinical trials the mean maximal decrease in heart rate after the first dose intake was seen 4 - 5 hours post-dose, with declines in mean heart rate, as measured by pulse, of 8 beats per minute for GILENYA 0.5 mg. The second dose may result in a slight further decrease. Heart rates below 40 beats per minute were rarely observed in patients on GILENYA 0.5 mg. Heart rate returned to baseline within 1 month of chronic dosing.

In the multiple sclerosis clinical program first-degree atrio-ventricular block (prolonged PR interval on electrocardiogram) was detected following drug initiation in 4.7% of patients on GILENYA 0.5 mg, in 2.8% of patients on intramuscular interferon beta-1a and in 1.5% of patients on placebo. Second degree atrio-ventricular block were detected in less than 0.5 % patients on GILENYA 0.5 mg. The conduction abnormalities were typically transient, asymptomatic and resolved within 24 hours on treatment. Although most patients did not require medical intervention one patient on the 0.5 mg dose received isoprenaline for an asymptomatic second degree atrio-ventricular block.

One case of transient third-degree atrio-ventricular block occurred three hours after the first dose of GILENYA 1.25mg was administered and lasted for 30 seconds. The patient recovered spontaneously.

Blood pressure

In multiple sclerosis clinical trials GILENYA 0.5 mg was associated with a mild increase of approximately 1 mmHg on average in mean arterial pressure manifesting after approximately 2 months of treatment initiation. This increase persisted with continued treatment. Hypertension was reported in 6.1% of patients on GILENYA 0.5 mg and in 3.8 % of patients on placebo.

Liver transaminases

In multiple sclerosis clinical trials, 8.5% and 1.9% of patients treated with GILENYA 0.5mg experienced asymptomatic elevation in serum levels of hepatic transaminases $\geq 3x$ ULN and $\geq 5x$ ULN, respectively, compared with corresponding figures in the placebo group of 1.7% and 1.0% respectively. The majority of elevations occurred within 6-9 months. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of GILENYA. In the few patients who experienced liver transaminase elevations $\geq 5x$ ULN

and who continued on GILENYA therapy, the elevations returned to normal within approximately 5 months.

Respiratory System

Minor dose-dependent reductions in FEV₁ and diffusing capacity of the lung for carbon monoxide (DLCO) values were observed with fingolimod treatment starting at month 1 and remaining stable thereafter. At month 24, the reduction from baseline values in percent of predicted FEV₁ was 3.1% for fingolimod 0.5 mg and 2.0% for placebo, a difference that resolved after treatment discontinuation. For DLCO the reductions at month 24 were 3.8% for fingolimod 0.5 mg and 2.7% for placebo.

Vascular events

Rare cases of vascular events which occurred in patients treated with GILENYA at higher doses (1.25 or 5.0 mg) include ischemic and haemorrhagic strokes, peripheral arterial occlusive disease and posterior reversible encephalopathy syndrome.

Lymphomas

Cases of lymphoma (cutaneous T-cell lymphoproliferative disorders or diffuse B-cell lymphoma) were reported in premarketing clinical trials in MS patients receiving GILENYA at, or above, the recommended dose of 0.5 mg. Based on the small number of reported cases and short duration of exposure, the relationship to GILENYA remains uncertain.

DOSAGE AND ADMINISTRATION

The recommended dose of GILENYA 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 GILENYA treatment, after the first dose, it is recommended that all patients be observed for a period of 6 hours for signs and symptoms of bradycardia (see **PRECAUTIONS, Bradyarrhythmia**).

Patients can switch directly from beta interferon or glatiramer acetate to GILENYA providing there are no signs of relevant treatment-related abnormalities e.g. neutropenia.

Children

GILENYA is not indicated for use in paediatric patients. (See **PHARMACOLOGY**).

The Elderly (≥ 65 years)

GILENYA should be used with caution in patients aged 65 years and over (see **PHARMACOLOGY**).

Patients with Renal Impairment

No GILENYA dose adjustments are needed (see **PHARMACOLOGY**).

Patients with Hepatic Impairment

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

Ethnicity

No GILENYA dose adjustments based on ethnic origin are needed (see **PHARMACOLOGY**).

Gender

No GILENYA dose adjustments are needed based on gender (see **PHARMACOLOGY**).

Diabetic patients

GILENYA should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular oedema (see **PRECAUTIONS**)

OVERDOSAGE

No cases of overdosage have been reported. However, single doses up to 80-fold the recommended dose (0.5mg) were well tolerated in healthy volunteers. At 40mg, 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 fingolimod from the body.

Contact the National Poisons Information Centre in Dunedin, New Zealand on telephone 0800 POISON or 0800 764766 for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

GILENYA 0.5 mg : white to almost white powder in white opaque body and bright yellow opaque cap gelatin capsules, size 3, radial imprint with black ink “FTY 0.5 mg” on cap and two radial bands imprinted on body with yellow ink.

Store below 30 degrees Celsius. Protect from moisture.

MEDICINE CLASIFICATION

Prescription Medicine

PACKAGE QUANTITIES

Pack of 28 capsules.

SPONSOR

Novartis New Zealand Limited
Private Bag 65904
Mairangi Bay
Auckland 0754
Building G, 5 Orbit Drive
Rosedale
Auckland 0632

Telephone: 09 361 8100

® = Registered Trademark

DATE OF PREPARATION

18 May 2011
