EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 June 2012
EMA/357270/2012

Assessment report for GILENYA

Review under Article 20 of **Regulation (EC) No 726/2004**

INN: fingolimod

Procedure number: EMEA/H/C/2202/A-20/008

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** ☐ww.ema.europa.eu
An agency of the European Union

Table of contents

1. Background information on the procedure

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

GILENYA (fingolimod) has been approved in Europe on 17 March 2011, through a centralised marketing authorization procedure in patients with highly active relapsing remitting multiple sclerosis. It is available as 0.5 mg oral hard capsules.

GILENYA has been approved in USA in September 2010 and is marketed in that country since 4 October 2010.

At the time of the initial marketing authorisation a cardiovascular effect was identified (from preclinical and clinical data) and included as an important risk in the Risk Management Plan (RMP).

In addition a recommendation to monitor patients for signs and symptoms related to bradycardia for at least six hours after the first dose was already included in the medicine's product information.

On 12 December 2011, the MAH informed the EMA of the occurrence, in the USA, of one case of sudden and unexplained death within 24 hours after GILENYA first dose. At that time three additional cases of sudden/unexplained deaths were reported in the Eudravigilance database for this product (with time to onset from 15 days to 3 months).

During the December 2011 meetings of PhVWP/CHMP a safety review of all cases of sudden/unexplained deaths and all cases of life threatening arrhythmias and conduction abnormalities with GILENYA was requested from the MAH. The MAH submitted the relevant data to the CHMP for further assessment on 21 December 2011. According to the requested safety review and the cases of cardiovascular disorders reported in the first European PSUR (covering the period from 1 March 2011 to 31 August 2011), a cardiovascular direct effect of fingolimod was suspected, mainly regarding the occurrence of unexplained sudden death, myocardial infarction, arrhythmias, conduction abnormalities (including atrioventricular (AV) blocks), hypertension (including hypertensive crisis).

The CHMP in its January 2012 plenary meeting discussed the issue and are in agreement that further information is required.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 18 January 2012 to assess the above concerns and its impact on the benefit/risk for GILENYA, and to give its opinion on measures necessary to ensure the safe and effective use of GILENYA and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

Oral explanation was provided by the MAH on 17 January 2012 and on 14 March 2012.

Additional information was provided by the MAH in writing on 10 January 2012.

In addition, the MAH and the CHMP agreed the wording of a Dear Healthcare Professional Communication (DHPC) designed to inform prescribers of GILENYA .

After reviewing all the available data submitted by the MAH to address the concerns discussed, the CHMP adopted an opinion 19 April 2012.

2. Scientific discussion

2.1. Introduction

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

GILENYA (fingolimod) has been approved in Europe on 17 March 2011, through a centralised marketing authorization procedure in patients with highly active relapsing remitting multiple sclerosis. It is available as 0.5 mg oral hard capsules.

At the time of the initial marketing authorisation a cardiovascular effect was identified (from preclinical and clinical data) and included as an important risk in the Risk Management Plan (RMP).

In addition a recommendation to monitor patients for signs and symptoms related to bradycardia for at least six hours after the first dose was already included in the medicine's product information.

During the December 2011 CHMP meeting a safety review of all cases of sudden/unexplained deaths and all cases of life threatening arrhythmias and conduction abnormalities with GILENYA was requested from the MAH. The MAH submitted the relevant data to the CHMP for further assessment on 21 December 2011. According to the requested safety review and the cases of cardiovascular disorders reported in the first European PSUR (covering the period from 1 March 2011 to 31 August 2011), a cardiovascular direct effect of fingolimod was suspected, mainly regarding the occurrence of unexplained sudden death, myocardial infarction, arrhythmias, conduction abnormalities (including atrioventricular (AV) blocks), hypertension (including hypertensive crisis).

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 18 January 2012 to assess the above concerns and its impact on the benefit/risk for GILENYA, and to give its opinion on measures necessary to ensure the safe and effective use of GILENYA and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

The CHMP reviewed all data available from the clinical studies and post-marketing experience which are hereafter being discussed.

2.2. Clinical safety

The MAH analysed and provided data on the cardiovascular disorders during the 24 hrs following the first dose. These data consisted of results of the clinical trials as well as post-marketing data.

i. Cardiovascular disorders during 24 hours following first dose of fingolimod (FTY720) and patient monitoring during the first 24 hours after the first dose administration

- **Data from clinical trials**

The following Table 1 provides data for patients that experienced cardiovascular disorders on day one and then again during the study (>2% in any treatment group) for all double-blind, randomised and controlled studies (D2201, D2301, D2302 and D2309 [Group D]). The percentage of patients with any cardiovascular disorder was comparable among the fingolimod and placebo groups. In the Interferon group only five patients had cardiovascular events on Day 1, but none of these patients had any cardiovascular event that occurred after Day 1.

Table 1: Number (%) of patients with cardiovascular disorders after Day 1 (>2% in any treatment group), by primary system organ class, preferred term and treatment Safety population (Group D: All double-blind, randomized and controlled studies) Subgroup of patients with cardiovascular disorders on Day 1

-Any primary system organ Class	FTY720 5 mg (N=7) n (%)	FTY720 1.25 mg (N=89) n (%)	FTY720 0.5 mg (N=49) n (%)	Placebo (N=18) n (%)	Interferon (N=5) n (%)
-Total	2 (28.6)	25 (28.1)	11 (22.4)	4 (22.2)	0 (0.0)
Cardiac disorders					
-Total	2 (28.6)	10 (11.2)	4 (8.2)	2 (11.1)	0 (0.0)
Palpitations	1 (14.3)	3 (3.4)	1 (2.0)	1 (5.6)	0 (0.0)
Atrioventricular block first degree	0 (0.0)	2 (2.2)	1 (2.0)	0 (0.0)	0 (0.0)
Tachycardia	1 (14.3)	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)
Investigations					
-Total	0 (0.0)	6 (6.7)	2 (4.1)	0 (0.0)	0 (0.0)
Blood pressure increased	0 (0.0)	5 (5.6)	1 (2.0)	0 (0.0)	0 (0.0)
Vascular disorders					
-Total	0 (0.0)	13 (14.6)	6 (12.2)	2 (11.1)	0 (0.0)
Hypertension	0 (0.0)	10 (11.2)	4 (8.2)	1 (5.6)	0 (0.0)
Hot flush	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)

The incidence of hypertension was higher in patients in the fingolimod (FTY720) groups compared to placebo (11.2% FTY720 1.25 mg, 8.2% FTY720 0.5 mg, 5.6% Placebo), but this is consistent with the higher incidence of hypertension noted in the overall study population in patients treated with fingolimod compared to Placebo or Interferon. Three patients in the fingolimod treatment groups had 1st degree atrioventricular (AV) block reported after Day 1 that were all mild in severity and did not require treatment. One of these patients had an adverse event of 1st degree AV block on Day 1, 1 patient had bradycardia and the other patient had an adverse event of increased PR interval on Day 1. Increased blood pressure was reported as an adverse event (AE) in 6 patients (5 [5.6%] FTY720 1.25 mg, 1 [2.0%] FTY720 0.5 mg, 0 placebo group). Three of the 6 patients with AEs of high blood pressure were treated with a drug or non-drug therapy, 4 cases were mild and 2 were moderate in severity. Heart palpitations were observed in a small number of patients and were comparable among the treatment groups.

An analysis of the risk of a cardiovascular disorder after day 1 was conducted in patients who had a first dose finding as compared to those who did not have a first dose finding in the combined double-blind, placebo-controlled studies in a total of 2355 patients (see table 2 below):

Table 2: Analysis of the risk of a cardiovascular disorder after 24 hours in patients who did or did not have a cardiovascular disorder on the day of the first dose

Table INF-1-1 (Page 1 of 1)
Analysis of the risk of a cardiovascular disorder after day 1, in patients who did or did not have a cardiovascular disorder on the day of first study drug intake
(Data from pool D; 2301 and 2309 combined, excl. 2302)
Safety population

			FTY720 1.25 mg (N= 799)	FTY720 0.5 mg (N= 783)	Placebo (N= 773)
RAW DATA					
Risk factor (RF=Yes) (N'= 103)			(n= 53)	(n= 34)	(n= 16)
	Event (Yes)	(M= 32)	18	10	4
	Event (No)	(M= 71)	35	24	12
Risk factor (RF=No) (N'= 2252)			(n= 746)	(n= 749)	(n= 757)
	Event (Yes)	(M= 444)	156	150	138
	Event (No)	(M= 1808)	590	599	619
MODEL ESTIMATES*					
OR(Risk factor)			1.95	1.66	1.50
95%-CI			[1.07; 3.53]	[0.78; 3.55]	[0.48; 4.71]
OR(Treatment)			1.19	1.12	
95%-CI			[0.92; 1.53]	[0.87; 1.45]	

WALD TEST	DF	Full model (p-value)	Reduced model (p-value)
-Study	1	0.9298	-
-Risk factor	1	0.0548	0.0392*
-Treatment	2	0.8786	0.6300
-RF*Treat	2	0.9957	0.9028
-Study*Treat	2	0.2317	-
-Stdy*Risk factor	1	0.1493	-
-Study*RF*Treat	2	0.4237	-

- *All estimates are from a (reduced) logistical regression model with Treatment, Risk factor as factors and a Treatment*Risk factor interaction. The full model investigates the between-study effect.
- Reference categories are RF=0, Treatment=comparator.

In the above table, all cardiovascular disorder AEs with onset date on or after start of study drug to 45 days after last dose of study drug and all cardiovascular disorder SAEs (irrespective of time after last dose of study drug) are included.

- Preferred terms are sorted within primary system organ class by frequency from highest to lowest in FTY720 1.25 mg group.
- A patient with multiple occurrences of an AE for a preferred term or system organ class under one treatment is counted only once in each specific category for that treatment.

In all treatment groups, the odds of a cardiovascular disorder after day 1 were significantly increased in patients who had a first dose finding as compared to those who did not have a finding. Considering the width of the confidence intervals, this increase was comparable in all three treatment groups. The odds were increased by a factor 1.66 [95%-CI: 0.78; 3.55] in the fingolimod 0.5 mg dose, and by a factor 1.50 [95%-CI: 0.48; 4.71] in placebo. There was no evidence of a significant treatment effect or an interaction; the increase in risk to experience a later cardiovascular disorder in patients who had a first-dose finding as compared to those who did not have a finding is comparable in patients treated with fingolimod 0.5 mg as in patients treated with placebo.

In order to further explore this issue, spontaneous reports on Day 1 from the post-marketing experience were retrieved up to a data cutoff of 23 Jan 2012. Of the 13 cases that had cardiac adverse events both on Day 1 and at a later time, 12 were HCP reported and 1 was non HCP reported. The majority of these cases with Day 1 events from the post-marketing setting reflected the negative chronotropic effect previously seen in clinical trials, reported as heart rate decreased on Day 1. Four patients had alterations in their blood pressure without any evidence of clinical symptoms on Day 1.

One patient experienced second degree AV block on Day 2, consistent with the known effect on AV conduction. This event was later interpreted as atypical Wenckebach block.

Of these 13 cases who had reported Day 1 events, some had a repeat similar cardiac adverse event (e.g. heart rate decreased, heart rate increased or heart rate findings like fluttering, premature ventricular contractions (PVC) or irregularity), most often in the first week or two of treatment. Other cases were confounded by concurrent illness at a later time point (e.g. severe diarrhea secondary to viral gastrointestinal illness, severe Multiple Sclerosis disability and autonomic instability). One fatality, due to an acute myocardial infarction on Day 32, had concurrent cardiac risk factors and autopsy findings of coronary atherosclerosis. She had experienced nadir heart rate (HR) of 47 on Day 1 without other problems. Overall, there was no pattern amongst the cases suggesting pre-existing risk factors that would predict cardiac adverse events at later time points. In addition, based on the available information, the later events, apart from the fatal MI, did not appear to be clinically significant or require intervention.

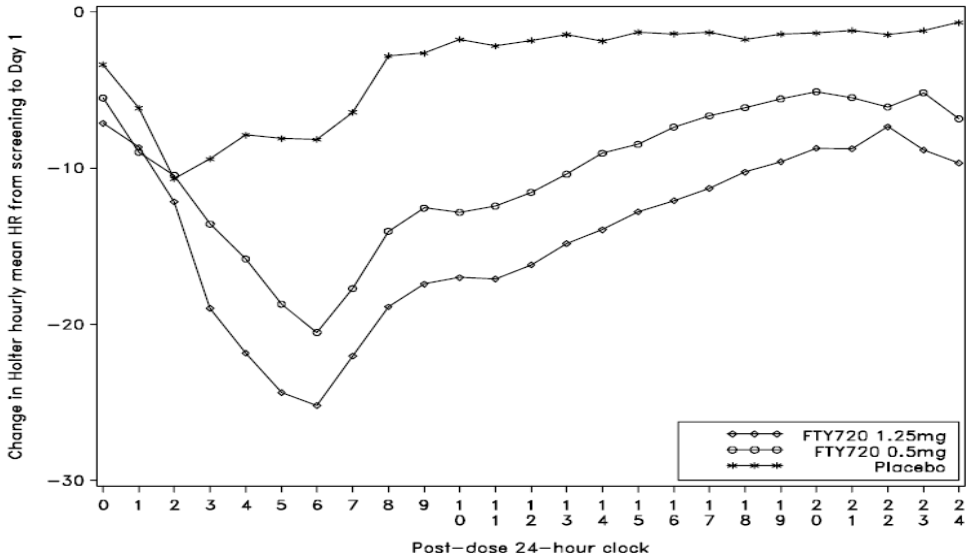
With respect to the management of potential serious cardiovascular disorders which may occur during the 24 hours following the first fingolimod dose, the recommendation in clinical trials was that atropine (SC or IV) be used, if necessary, as the first-line treatment of bradycardia, up to a maximum daily dose of 3 mg. However, most of the bradyarrhythmias in clinical trials have been either asymptomatic or associated with only minor symptoms which did not require pharmacological intervention. There have, however, been rare episodes of symptomatic bradycardia, including several episodes of syncope. The most severe episodes have been temporally associated with vagal stimuli such as nausea, blood drawing, or vomiting. This raises the possibility of an interaction between autonomic nervous system dysfunction with vagal hyperactivity and fingolimod in susceptible individuals.

- **Monitoring during 24 hours following administration of the first dose**

Holter hourly heart rate

A total of 1080 patients from study D2309 were included in the Holter ECG analysis set. The changes in hourly mean heart rate on the first day of treatment compared to the same daily hours at the screening Holter ECG (i.e. adjusting by circadian rhythm) are shown graphically in figure 1.

Figure 1: Change in Holter hourly mean heart rate (bpm) from screening to Day 1 by post-dose 24-hour clock (Study D2309)



Hour 0 refers to the last non-missing assessment prior to the first dose on day 1.
Holter hourly mean heart rates at day 1 are compared with the same hour of the day at screening.
Post-dose 24-hour clock is defined using the first dose time of day 1. HR = heart rate
Source: PT-Figure 14.3-1.1

A similar decline in hourly mean heart rate was observed in the FTY720 and placebo groups in the first 2 hours post-dose on day 1. Thereafter, the change in hourly mean heart rate from screening to day 1 continued to decrease in both FTY720 groups reaching maximal mean decreases at 6 hours post-dose of 25.2 bpm for FTY720 1.25 mg and 20.5 bpm for FTY720 0.5 mg. This effect attenuated (i.e. heart rate increased) over the following 18 hours. At 24 hours post-dose, the mean decrease from screening in hourly mean heart rate was reduced to 9.3 bpm in the FTY720 1.25 mg group and 6.9 bpm in the FTY720 0.5 mg group.

Patients in the placebo group, exhibited an initial decline in hourly mean heart rate in the first 2 hours post-dose on day 1 versus screening to a maximal mean decrease of 10.7 bpm at 2 hours, followed by a gradual increase in heart rate returning close to baseline values by 10 hours post-dose and remaining at that level for the rest of the 24-hour monitoring period.

In the following table the results of monitoring of patients during the phase III placebo-controlled (D2309) as well from all studies are presented. It is shown that the majority of the treated patients were discharged at 6 hours following the first dose administration.

Table 3: Treatment initiation experience

	Phase III placebo-controlled (D2309)			All studies	
	Placebo	Fingolimod		Fingolimod	
	N=355	0.5 mg N=357	1.25 mg N=370	0.5 mg N=1640	1.25 mg N=1642
Discharge at 6 hours	347 (97.7)	306 (85.5)	299 (80.8)	1390 (84.8)	1305 (79.5)

Extended monitoring	8 (2.3)	52 (14.5)	70 (18.9)	200 (12.2)	285 (17.4)
Hospitalised	-	-	9 (2.4)	18 (1.1)	41 (2.5)
Treated	-	-	2 (0.5)	1* (0.1)	7 (0.4)
Drug discontinued	1 (0.3)	1 (0.3)	5 (1.4)	3 (0.2)	21 (1.3)

Discharge criteria: HR >50 bpm, >80% of baseline and must not be lowest value
No symptomatic bradycardia
No new significant ECG abnormalities

*Isoprenaline use for an asymptomatic transient 2nd degree AV block Mobitz I with lowest HR of 46 bpm

The CHMP recommendation for the first-dose monitoring is that all patients should have an ECG and blood pressure measurement performed prior to the first dose of fingolimod. 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 also recommended by the CHMP.

- **Post-marketing data**

With respect to second- and third-degree atrioventricular block in the post-marketing setting, as of 12 December 2011 (data cutoff date), a total of 25 events (in 24 patients) including 5 events of 3rd-degree atrioventricular block (4 were not confirmed on review of the ECGs, 1 case confirmed), 17 events of 2nd-degree atrioventricular block (2 type II, 9 type I, one 2:1, one 3:1 and 4 with type unspecified) and 3 events of atrioventricular block – type unspecified were reported. All 25 events occurred within 6 hours of receiving the first dose of fingolimod. Two patients had taken a calcium channel blocker and/or a beta blocker as concomitant medications (one experienced 2nd-degree AV block, the other one experienced AV block-type unspecified, both events were asymptomatic and resolved without any treatment). Three patients received atropine for bradycardia (two were symptomatic, all events resolved). Outcome of the events included complete recovery in the majority of cases (24) with one case where outcome was not reported (1, event: AV block-unspecified).

The only significant bradyarrhythmic event that has been reported during Day 1 after the 6- hour observation is the case of transient asystole occurring 21 hours post-dose initiation. The history and ECG findings could suggest a vagal stimulus as contributing to the event, which spontaneously reversed.

The patient who died 24 hours after the first dose remains without a specific diagnosis, although it is recognised that the patient had potential risk factors for cardiac adverse events including hypertension and concomitant use of a beta blocker and a dihydropyridine calcium channel blocker medication.

In terms of other potential bradyarrhythmias, although several have been noted with fingolimod, they have also been equally common in the control groups and not limited in either fingolimod or control groups to Day 1.

Conclusions on monitoring after first dose administration

During clinical studies (Group D, all double blind randomised and controlled studies), proportion of patients with a cardiovascular disorder on day 1 who also experienced another cardiovascular disorder after day 1 was respectively of 28.6%, 28.1, 22.4, 22.2 and 0 in the fingolimod 5 mg, 1.25 mg, 0.5 mg, placebo and interferon groups. On the basis of the statistical analysis regarding the risk of a

cardiovascular disorder after day 1 in patients with cardiovascular disorder at day 1 compared to patients without a cardiovascular disorder at day 1, no clear conclusion could be drawn. However, the number of patients with cardiovascular disorders at day 1 was low.

The MAH also provided post-marketing data. Thirteen fatal cases have been retrieved by the MAH, with a cardiovascular disorder on day 1 and a cardiovascular disorder after day one. The thirteen cases retrieved by the MAH occurred in 9 female patients and 4 male patients, with a mean age of 44 years (extremes 26 -61). Most of the deaths and cardiovascular problems had occurred in patients with a history of cardiovascular problems and/or taking other medicines. In 9 cases, a decrease in heart rate was reported at day 1 (with blood pressure increase in 1 case, and blood pressure decrease in 2 cases). In 2 of those 9 cases, a heart rate decrease was also reported, respectively after 14 days of treatment (with a reported heart rate of 32 bpm) and after 84 days of treatment (with a reported heart rate of 30 bpm, and an associated blood pressure decrease). The third case reported syncope and loss of consciousness at day 8. The fourth case of heart rate decreased at day 1 reported fatal myocardial infarction at day 32. Of the 5 remaining cases of heart rate decrease at day 1, one reported an irregular heart rated at day 5, and 4 blood pressure disorders (fluctuation in one case, increase in 2 cases, and decrease in one case). Additional two fatal cases of patients with cardiovascular adverse events were also reported thereafter, making the total cases to 15. Although the cause of these latest events is still not known, these patients were treated with Gilenya and additionally had known cardiovascular problems.

No clear pattern emerged from the post-marketing cases reported and no definite conclusion can be drawn on the basis of those cases.

Based on evaluation of these data, the incidence of overall blocks is low (~ 1 per 1000) with a small number of high degree atrioventricular blocks (e.g. Mobitz Type II 2nd-degree AV block, complete heart block) reported. The nature of the events (e.g. onset time, course and outcome) is consistent with previous cumulative experience on 1st-dose cardiac adverse events with fingolimod. Clinical trial and post-marketing data provided do not allow concluding on a potential predictive effect of first dose related cardiovascular disorders for delayed cardiovascular disorders.

However, health care professionals should be better informed, with in particular, mention in section 4.4 of the summary of product characteristics (SmPC) that negative chronotropic effect of fingolimod, observed during hours following first intake, can be reversed if necessary, by parenteral atropine or isoprenaline (as it is already mentioned in section 5.1 of the currently approved SmPC).

The occurrence of 3rd-degree AV block with the approved dose of 0.5 mg is newly observed (previously only reported with 1.25mg) and the CHMP proposes its inclusion in the product information and in section 4.4 and 4.8 of the SmPC.

Following the assessment of the above data and in order to further strengthen procedures to enhance patient safety the CHMP recommended changes in the SmPC to include the safety information on cardiovascular concerns in the relevant sections. More specifically the CHMP recommended that a continuous 6 hour monitoring using electrocardiography (ECG) after administration of the first dose needs to be in place during the first dose monitoring. The first dose monitoring procedure is recommended for every patient who is initiated with fingolimod or re-initiated after an interval of at least 15 days. In addition if there are any concerns the monitoring may need to be extended until the symptoms cease to exist.

ii. Cardiovascular disorders during medication and in at risk patients

Data from Clinical studies

- **Study D2316**

The cardiovascular (CV) profile of fingolimod in patients with relapsing-remitting MS has been investigated in the clinical Phase II and III program. The Phase IIIb study D2316, a 4-month, open-label, single-arm study of fingolimod in patients with relapsing MS, included a broader population of patients than previously exposed to fingolimod in clinical trials: upper age limit of 65 years; and controlled diabetes, chronic asthma, and certain protocol-defined cardiac risk factors.

This study included a total of 2417 patients of whom a subgroup of 295 patients met protocol-defined criteria for coexistent cardiovascular risk factors at baseline (baseline heart rate of 45-54 bpm (<45 bpm was exclusion criterion), second-degree AV-block (Mobitz I), history of recurrent symptomatic bradycardia, concomitant treatment with beta blockers).

After assessing the submitted data from the study D2316, only 295 patients were considered to be at cardiac risk, defined as either bradycardia at rest (heart rate 45-54), history of symptomatic bradycardia, of second-degree AV block, vasovagal syncope or co-medication with beta-blockers and/or calcium channel blockers. Only 26 patients had diabetes, and 80 were older than 56 years. The overall population was therefore at a low cardiovascular risk.

During the study, the incidence of cardiac disorders was not clearly higher in patients with cardiac risk (5.1%) than in the other patients (4.1%). The incidence of cardiac disorders during the first 2 days following fingolimod first administration was 2.4% in the cardiac risk group, and 2.0% in the rest of the population. Bradycardia was the most common cardiac adverse effect (1.4% in the patients with cardiac risk factors versus 0.5% in patients without risk factors), with palpitations (0 in patients with risk factors versus 0.7% in patients without risk factors). There were 6 reports of AV block, all in the population without cardiac risk factors.

The incidence of cardiac disorders (mostly bradycardia) was 9% in patients with beta blockers and/or calcium channel blockers versus 3.9% in patients without. And at day 1 and/or 2, those incidences were respectively of 6.1% versus 1.9%.

Results in patients monitored on-site (whether at cardiac risk or not), are in favour of a clear bradycardic effect of fingolimod: while heart rate <45 was observed in only 3 patients before first dose on day 1, it was observed in 16 patients during the 6 post-dose hours. Similarly, heart rate 45-55 was observed in 56 patients pre-dose, and in 179 after first dose.

Regarding Holter monitoring, overall, more cardiac disorders were recorded during screening than during day 1, after fingolimod first dose. The only exceptions were Mobitz 1 2nd degree AV block in patients without cardiac risk factors (2 cases screening, 22 post-dose), and 2:1 AV block, both in patients with and without cardiac risk factors. Although patients with cardiac risk factors had obviously more cardiac disorders at screening, the increase in AV block or bradycardia was not more common in these patients.

Of note, two female patients, aged respectively 30 years old and 49 years old, presented angina pectoris during the study, with as only reported symptoms: pain extending to left arm in one case, and cardiac chest pain in the second case.

Given the limited data regarding patients with cardiac risk factors and in the absence of a comparator, no conclusion can be drawn up to date on the basis of this study. However, patients concomitantly receiving beta blockers and calcium channel blockers seem to be at increased risk of cardiac disorders.

- **Other clinical trial data**

The analysis of clinical trial data for CV adverse events in patients with and without CV disease/risk factors was based on the following groupings:

Group D: All patients in double-blind, randomised and controlled studies: D2201 (6- month vs. placebo, D2301 (24 months vs. placebo), D2302 (12-month vs. interferon (IFN) beta-1a), D2309 (24 months vs. placebo).

Extended Group E (fingolimod treated safety population): All fingolimod treated patients in either double-blind, randomised and placebo- or active- controlled studies (D2201, D2301, D2302 and D2309) or in their extension phases (D2201E1, D2301E1, D2302E1 and D2309E1). Data from the ongoing extension study D2309E1 are included with a cut-off date of 31 March 2011.

CV adverse events were summarised for the overall populations in Group D and Extended Group E and for subgroups of patients with and without medical history of CV disease and/or risk factors. Events with onset on Day 1 (within 24 hours of first dose) and events with onset after Day 1 (at any time) were summarised separately.

The number of CV adverse events reported on Day 1 was small overall, compared to the placebo and IFN beta-1a groups (1.2-1.5%). Based on the known effect of fingolimod on heart rate and conduction upon treatment initiation, bradycardia and atrioventricular (AV) blocks (1st and 2nd degree) were the most frequently reported events in the fingolimod groups on Day 1.

When analysing the data from the groups of patients with and without cardiovascular diseases and/or risk factors, the largest subgroup was the one in which patients did not have any CV disease or a risk factor reported in their medical history. Higher rates of CV adverse events were reported in the subgroups of patients with a medical history of CV disease/risk factors compared to those without. This was seen in the fingolimod groups as well as in the placebo group.

As expected, higher numbers of patients with CV adverse events were reported in the fingolimod groups, with evidence of a dose-effect, compared to the control groups. This was seen in all subgroup analyses, although interpretation of the results for some of the subgroups is difficult due to the very small number of cases reported..

Following the CHMP request, the MAH provided listings with details, by preferred term of cardiovascular diseases and risk factors identified.

For group D patients with risk factors for cardiovascular disease were mostly patients with hypercholesterolemia, hyperlipidaemia and obesity. No increase incidence of cardiac disorders has been observed in those patients compared to patients without cardiovascular diseases or risk factors. Patients with cardiovascular diseases at baseline, included in FTY720 1.25 mg, 0.5 mg and placebo groups experienced a higher incidence of cardiac disorders compared to patients without cardiovascular diseases and without risk factors. It should be noted that those patients with cardiovascular diseases at baseline were mostly patients with valve disorders and controlled hypertension.

In the Extended Group E population, the proportion of patients with CV adverse events with onset on Day 1 was consistent with what was seen for Group D for fingolimod treated patients. Findings in subgroups of patients with and without cardiovascular diseases and/or risk factors were consistent with those reported for fingolimod treated patients in Group D.

The proportion of cardiovascular adverse events with onset after day 1 was similar across the fingolimod (13.8-17.4%) and placebo groups (16.5%) and slightly lower in the interferon beta group (9.5%). In the SOCs Cardiac disorders and Investigations, events were reported at similar frequencies

in the fingolimod and placebo groups. In the Vascular disorders SOC, more events were reported in the fingolimod groups compared to the control groups. This was mainly driven by the higher frequency of reports of hypertension in the fingolimod groups (6.4-7.8% vs. 2.1-3.2% in the control groups).

Except for patients with CV disease and risk factors, the overall number of CV adverse events reported after Day 1 in the subgroups was not higher in the fingolimod groups compared to the placebo group. A higher rate of hypertension in patients on fingolimod vs. placebo was observed.

For patients with cardiovascular diseases and risk factors (i.e. mostly with hypercholesterolemia, hyperlipidemia and obesity), a higher incidence of cardiovascular adverse events as defined above (32-44% for fingolimod 0.5 mg and 1.25 mg vs. 19.5% for placebo), and in particular of hypertension has been observed, for all groups of patients, included patients in the placebo and Interferon groups.

- **Post-marketing experience for patients with CV disease or risk factors**

In the post-marketing setting, a search of the MAH's safety database (data cutoff: 23 Jan 2012) was conducted using the same search criteria as used for clinical trial cases above using MedDRA version 14.1. The search retrieved a total of 185 cases with CV disease/other risk factors that experienced cardiovascular adverse events while being treated with fingolimod.

Data on the CV adverse events and time of onset after starting therapy that occurred in patients who had history of CV disease / risk factors is provided in Table 4 below.

Table 4: Patients with cardiovascular diseases or risk factors that had cardiovascular adverse events – event description

			Onset of CV Adverse Events				
Risk Factor	**PT**	**Total**	**Day 1**	**Day 2-10**	**Day 11-30**	**>30 Days**	**Unknown**
CV Disease (n=116)	Bradycardia	42	31	3	1	3	4
	AV Block	13	12	-	-	-	1
	Hypertension	29	7	3	4	7	8
	Hypotension	12	7	1	3	-	1
	Arrhythmia	5	1	2	2	-	-
	Abnormal ECG	7	3	1	1	2	-
	Myocardial infarction	2	1	1	-	-	-
	HR increased	3	-	-	-	2	1
	Atrial Fibrillation	1	-	-	-	1	-
	Cardiac disorder NOS	2	-	-	-	1	1
Other Risk Factors (n=18)	Bradycardia	9	9	-	-	-	-
	AV Block	1	1	-	-	-	-
	Hypertension	4	-	2	-	1	1
	Hypotension	2	2	-	-	-	-
	Myocardial infarction	1	-	-	-	1	-
	HR increased	1	-	-	1	-	-
CV Disease with other risk factors (n=51)	Bradycardia	12	8	-	1	2	1
	AV Block	7	7	-	-	-	-
	Hypertension	14	3	1	-	6	4
	Hypotension	7	3	-	2	1	1
	Arrhythmia	2	1	-	-	1	-

	Abnormal ECG	1	-	-	-	1	-
	Myocardial infarction	3	-	-	-	3	-
	HR Increased	4	-	-	1	2	1
	Bundle branch block	1	-	-	-	1	-
Total		185	96	14	16	35	24

The majority of the CV adverse events experienced by patients who had a history of CV disease/other risk factors were the typical events associated with fingolimod, i.e. bradycardia, AV blocks and hypertension. Regarding the time of onset, 60% of events with known onset begin on Day 1 with only approximately 20% starting after Month 1.

Bradycardia and AV block events account for approximately 45% of all events and 87% of those with known onset date occurred on Day 1. Hypertension was reported in 25% of patients. Of late-occurring events hypertension represented 40% of the cases.

Of the 96 patients who experienced cardiovascular adverse events on Day 1 of initial fingolimod intake, the events that could be considered more severe included 3 complete AV blocks, 2 second-degree AV blocks (Mobitz II) and 1 myocardial infarction with a favourable outcome.

Of the 89 patients who experienced cardiovascular adverse events after Day 1 of initial fingolimod intake, the events that could be considered more severe included 5 myocardial infarctions (2 were fatal and 1 case of atrial fibrillation. There was also a case of fatal hypertensive cardiovascular disease.

Conclusions on cardiovascular adverse *events in at risk patients*

Based on current clinical and post-marketing data no clear increase of cardiovascular disorders under fingolimod in patients with cardiovascular disease and/or risk factors can be defined at Day 1 and after Day 1, except for “hypertension”. However, data analyses were based on limited number of patients, and baseline cardiovascular diseases and risk factors identified by the MAH mainly included patients with hypertension, cardiac valve disorders, hyperlipidaemia, hypercholesterolemia, and obesity.

No clear data were available for patients who were excluded from participating to clinical studies.

The CHMP therefore recommended the amendments to the SmPC and especially section 4.4 “Warnings and precautions of use” in order to include the information on patients with pre-existing CV adverse events as well on “hypertension”.

Due to the risk of serious rhythm disturbances, the CHMP agreed that Gilenya should not be used in patients at risk. These patients may be with second degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial heart block, in patients with a history of symptomatic bradycardia or recurrent syncope, or patients with significant QT prolongation (QTc>470msec (female) or >450msec (male)).

In addition since significant bradycardia may be poorly tolerated in patients with known ischaemic heart disease (including angina pectoris), cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension or severe untreated sleep apnoea, then the medicinal product should not be used in these patients. Furthermore, if treatment is considered in such patients, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring (at least overnight) for treatment initiation.

The CHMP also recommended that clear communications to practitioners regarding these risks, including recommendations regarding cardiology consultation and closer observation during initial dosing, including overnight observation if necessary, will enhance patient safety.

iii. Concomitant use of fingolimod with beta-blockers or calcium channel blockers

The MAH submitted data on current clinical pharmacology, clinical and post-marketing data in combination with heart rate lowering drugs or QT prolonging drugs.

- **Atenolol**

Study A0114 was a cross-over designed study in which healthy volunteers (n=14) received fingolimod 5 mg single dose or atenolol 50 mg daily for four days or both treatments together.

Fingolimod versus atenolol. The mean heart rate nadir was significantly lower by 8% for fingolimod compared with atenolol (p = 0.03), but the fingolimod/atenolol ratio and 90% confidence interval remained in the equivalence bounds: 0.92 (0.86-0.98).

None of the other cardiovascular responses were different between treatments with fingolimod/atenolol ratios for heart rate $AUEC_{(0-12)}$ of 0.97 (0.92-1.03); for mean arterial pressure nadir of 1.02 (1.00-1.04); and for mean arterial pressure $AUEC_{(0-12)}$ of 1.02 (1.00-1.04).

Fingolimod versus fingolimod + atenolol. Fingolimod 5 mg + atenolol decreased heart rate responses by 15% and mean arterial pressure responses by 7-8% compared with fingolimod 5 mg alone.

With one minor exception, however, all ratios and 90% confidence interval remained in the standard equivalence bounds as follows: heart rate nadir 0.85 (0.79-0.92); heart rate $AUEC_{(0-12)}$ 0.85 (0.81-0.89); mean arterial pressure nadir 0.93 (0.91-0.96); and mean arterial pressure $AUEC_{(0-12)}$ 0.92 (0.90-0.95).

Although the heart rate and mean arterial pressure trajectories were shifted downward on the measurement scale after fingolimod 5 mg + atenolol, they retained their normal circadian patterns.

- **Diltiazem**

Study A0114 was a cross-over designed in which study healthy volunteers (n=14) received fingolimod 5 mg single dose or diltiazem extended release 240 mg daily for four days or both treatments together.

Fingolimod 5 mg versus diltiazem. The mean heart rate nadir and the $AUEC_{(0-12)}$ were significantly lower by 18% and 13% for fingolimod compared with diltiazem (p <0.001). The corresponding fingolimod/diltiazem ratios and the 90% confidence intervals were: 0.82 (0.78-0.85) and 0.87 (0.84-0.90). Mean arterial pressure nadir and $AUEC_{(0-12)}$ were similar between treatments: 1.00 (0.97-1.04) and 0.98 (0.96-1.01).

Fingolimod 5 mg versus fingolimod 5 mg + diltiazem. Heart rate and mean arterial pressure responses were not different from fingolimod 5 mg alone compared with fingolimod 5 mg + diltiazem. The ratios and 90% confidence intervals were 0.99 (0.94-1.05) for heart rate nadir, 0.98 (0.95-1.00) for heart rate $AUEC_{(0-12)}$, 1.00 (0.96-1.03) for mean arterial pressure nadir, and 0.98 (0.96-1.01) for mean arterial pressure $AUEC_{(0-12)}$. The heart rate trajectory after fingolimod + diltiazem retained a normal circadian pattern.

The CHMP considered the data submitted by the MAH and concluded that fingolimod enhances heart rate decrease due to atenolol, as seen when either comparing atenolol vs fingolimod (HR lower than 8% with the latter) or adding atenolol to fingolimod (the combination decreases HR by 15%, comparatively to 7 to 8% with fingolimod).

The heart rate trajectory and mean arterial pressure were shifted downward, despite normal circadian rhythms. So the lack of clinically relevant interaction with beta-blockers cannot be agreed on, whereas there is an additive effect on HR of 15%, when comparing fingolimod alone to fingolimod plus atenolol. The negative chronotropic effect of fingolimod alone is 7-8% stronger than that of atenolol alone. Even if it did not translate into noticeable events in healthy volunteers, this additive effect, although not systematic as shown by the lack of outliers, may give raise to isolated/unexpected/undesirable events in the clinical setting, occurring later than the 6 hours-period after dosing, and notably during the late-night bradycardia.

It is noted that the effect of diltiazem on heart rate is minor, compared to that of atenolol. However, given the strong depressor cardiac propertiesof calcium channel blocker, starting fingolimod in patients who take calcium channel blockers is not recommended.

Conclusions on agents inducing bradycardia

Considering that the bradycardia-inducing effect of atenolol is similar to that of fingolimod, the current warning needs to be reinforced. Knowing that beta-blocking treatment cannot be abruptly interrupted and impairs/prevents compensative adrenergic reactions in case of AV block or collapse, considering also that night-late bradycardia is a unpredictable, obvious additional risk, bradycardia-inducing drugs, including anticholinesteratics, should be avoided in patients starting fingolimod treatment. If the combination is deemed necessary, advice from a cardiologist should be sought and at least overnight monitoring should be recommended.

Considering that beta-blockers cannot be abruptly interrupted, the potentiating of beta-blockers by fingolimod in healthy volunteers, the subsequent loss of sympathetic compensative reactions in case of abrupt bradycardia, the circadian reduction in heart rate at night, these elements require a reinforcement of the warning in the SmPC.

For that the CHMP recommended that the section 4.4, “Special warnings and precautions for use” and section 4.5 “Interaction with other medicinal products and other forms of interaction “of the SmPC be revised to include the information on agents inducing bradycardia as experience with fingolimod is limited in patients receiving concurrent therapy with beta blockers, heart rate lowering calcium channel blockers (such as diltiazem), or other substances which may decrease heart.

Moreover, since the initiation of treatment is also associated with slowing of the heart rate, concomitant use of these substances during treatment initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate treatment should not be initiated in patients who are concurrently treated with these substances. The CHMP recommended that if treatment is considered in such patients, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products or appropriate monitoring for treatment initiation (at least overnight) if the heart-rate-lowering medication cannot be stopped.

v. Hypertension

In multiple sclerosis clinical studies 0.5 mg fingolimod was associated with an average increase of approximately 3 mmHg in systolic pressure and approximately 1 mmHg in diastolic pressure, manifesting approximately 1 month after treatment initiation. This increase persisted with continued

treatment. Hypertension was reported in 6.1% of patients on fingolimod 0.5 mg and in 3.8% of patients on placebo. Onset of hypertension can occur within 1 month of treatment and hypertension as an adverse event has been reported on the day of treatment initiation.

Taking into account this information as well as the recent post-marketing observations (see table 4 above) the CHMP recommended that treatment with fingolimod should not be initiated in patients with uncontrolled hypertension until this is brought under control.

Conclusions on Safety

The MAH provided safety data from clinical studies. During these studies (double blind randomised and controlled studies, D2201, D2301, D2302 and D2309 [Group D]), the proportion of patients with a cardiovascular disorder on day one who also experienced another cardiovascular disorder after day one was respectively of 28.6%, 28.1, 22.4, 22.2 and 0 in the fingolimod 5 mg, 1.25 mg, 0.5 mg, placebo and interferon groups. On the basis of the statistical analysis regarding the risk of a cardiovascular disorder after day one in patients with cardiovascular disorder at day one compared to patients without a cardiovascular disorder at day one, no clear conclusion could be drawn. However, the number of patients with cardiovascular disorders at day one was low but still more than 2% in any treatment group.

This safety review of Gilenya was initiated following receipt of a spontaneous report of a 59 year-old female patient with multiple sclerosis who died within 24 hours of taking the first dose of Gilenya and was also treated for hypertension. So, the MAH provided post-marketing data on all cardiovascular adverse events received. Thirteen fatal cases have been retrieved by the MAH, with a cardiovascular disorder on day one and a cardiovascular disorder after day one. The thirteen cases retrieved by the MAH occurred in 9 female patients and 4 male patients, with a mean age of 44 years. In 9 cases, a decrease in heart rate was reported at day one (with blood pressure increase in 1 case, and blood pressure decrease in 2 cases). In 2 of those 9 cases, a heart rate decrease was also reported, respectively after 14 days of treatment (with a reported heart rate of 32 bpm) and after 84 days of treatment (with a reported heart rate of 30 bpm, and an associated blood pressure decrease). One third case, reported syncope and loss of consciousness at day 8. A fourth case of heart rate decreased at day one reported fatal myocardial infarction at day 32. Of the 5 remaining cases of heart rate decrease at day one, one reported an irregular heart rated at day 5, and 4 blood pressure disorders (fluctuation in one case, increase in 2 cases, and decrease in one case). Additional two fatal cases of patients with cardiovascular adverse events were also reported there after, making the total cases to 15. Although the cause of these latest events is still not known, these patients were treated with Gilenya and additionally had known cardiovascular problems.

It is acknowledged that initiation of fingolimod 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, as this information was already in the product information of Gilenya since the initial marketing authorisation.

On the basis of the available data the CHMP agreed that after the first dose, the decline in heart rate starts within one hour and is steepest within 6 hours. The negative chronotropic effect of fingolimod persists beyond 6 hours and progressively attenuates over subsequent days of treatment. With continued administration, heart rate returns to baseline within one month. Conduction abnormalities were typically transient and asymptomatic. They usually did not require treatment and resolved within the first 24 hours on treatment. The CHMP recommended that should post-dose bradyarrhythmia-related symptoms occur, appropriate clinical management should be initiated and monitoring should be continued until the symptoms have resolved. Should a patient require pharmacologic intervention

during the first-dose observation, at least overnight monitoring in a medical facility should be instituted.

In addition, the CHMP concluded that since significant bradycardia may be poorly tolerated in patients with known ischaemic heart disease (including angina pectoris), cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension or severe sleep apnoea, the medicinal product should not be used in these patients. Furthermore, if treatment is considered in such patients, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring (at least overnight) for treatment initiation.

Considering that the bradycardia-inducing effect of beta-blockers is similar to that of fingolimod, the CHMP recommended that the current warning in the product information needs to be reinforced. Knowing that beta-blocking treatment cannot be abruptly interrupted and impairs/prevents compensative adrenergic reactions in case of AV block or collapse, considering also that night-late bradycardia is unpredictable, bradycardia-inducing drugs, including anticholinesteratics, should be avoided in patients starting on fingolimod. If the treatment combination is deemed necessary, an extended monitoring, at least overnight, should be recommended. For that the CHMP recommended that the section 4.4, “Special warnings and precautions for use” and section 4.5 “Interaction with other medicinal products and other forms of interaction“ of the summary of product characteristics (SmPC) be revised to include the information on agents inducing bradycardia as eexperience with fingolimod is limited in patients receiving concurrent therapy with beta blockers, heart rate lowering calcium channel blockers (such as diltiazem), or other substances which may decrease heart rate.

Moreover, since the initiation of treatment is also associated with slowing of the heart rate, concomitant use of these substances during treatment initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate treatment should not be initiated in patients who are concurrently treated with these substances. The CHMP recommended that if treatment is considered in such patients, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products or appropriate monitoring for treatment initiation (at least overnight) if the heart-rate-lowering medication cannot be stopped.

The CHMP also assessed the incidents of hypertension in multiple sclerosis clinical studies. The 0.5 mg dose of fingolimod was associated with an average increase of approximately 3 mmHg in systolic pressure and approximately 1 mmHg in diastolic pressure, manifesting approximately 1 month after treatment initiation. This increase persisted with continued treatment. Hypertension was reported in 6.1% of patients on fingolimod 0.5 mg and in 3.8% of patients on placebo. Onset of hypertension can occur within 1 month of treatment and hypertension as an adverse event has been reported on the day of treatment initiation.

Taking into account this information as well as the recent post-marketing observations the CHMP recommended that treatment with fingolimod should not be initiated in patients with uncontrolled hypertension until this is brought under control.

Risk management plan

The MAH submitted an updated Risk Management Plan within this procedure which included a risk minimisation plan. The summary of the risk management plan is in the table 5 below. The changes made following this article 20 review procedure are presented in grey shading. In addition the MAH will submit an updated RMP by the end of April 2012 together with the scheduled PSUR submission.

Table 5: Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risks		
Bradyarrhythmia (including conduction defects) occurring post-first dose	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2316: 4-month, open-label, multi-center study to explore tolerability and safety and health outcomes of FTY720 in patients with relapsing forms of MS Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Proposed substudy: currently being planned with the primary objective of estimating the incidence of cardiovascular adverse events in fingolimod treated patients who experienced a bradyarrhythmic event that led to extended monitoring during treatment initiation of fingolimod vs. patients treated with a DMT. Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy. Study FTY720D2121: A double blind, placebo controlled, parallel group study to investigate two different dose-titration regimens of fingolimod on the negative chronotropic effect of fingolimod in healthy subjects Targeted follow-up of all serious spontaneous reports using a targeted cardiac rate and rhythm disorders checklist (including first dose observation)	Risk addressed in SmPC sections 4.4 and 4.8 and derived local labels: SmPC Sections 4.4 and 4.8 state that initiation of fingolimod 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. After the first dose, the decline in heart rate starts within one hour and is steepest within 6 hours. The negative chronotropic effect of Gilenya persists beyond 6 hours and progressively attenuates over subsequent days of treatment. With continued administration, heart rate returns to baseline within one 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 fingolimod 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 Gilenya. 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 bradyarrhythmia-related symptoms occur, appropriate clinical management should be initiated and monitoring should be continued until the symptoms have resolved. Should a patient require pharmacologic intervention during the first dose monitoring, overnight monitoring in a medical facility should be instituted.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		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, 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). Due to the risk of serious rhythm disturbances, Gilenya should not be used in patients with second degree Mobitz type II or higher AV block, sick-sinus syndrome, sino-atrial heart block, a history of symptomatic bradycardia or recurrent syncope, or in patients with significant QT prolongation (QTc >470 msec (females) or >450 msec (males)). Since significant bradycardia may be poorly tolerated in patients with known ischaemic heart disease, (including angina pectoris), cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension, or severe untreated sleep apnoea, Gilenya should not be used in these patients. In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks. If treatment 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 Gilenya has not been studied in patients with arrhythmias requiring treatment with Class Ia (e.g. quinidine, disopyramide) or

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		Class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products. Class Ia and Class III antiarrhythmic medicinal products have been associated with cases of torsades depointes in patients with bradycardia. Since initiation of Gilenya treatment results in decreased heart rate, Gilenya should not be used concomitantly with these medicinal products. Experience with Gilenya is limited in patients receiving concurrent therapy with 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, anticholinesteratic agents or pilocarpine). Since the initiation of Gilenya treatment is also associated with slowing of the heart rate (see "Bradyarrhythmia"), concomitant use of these substances during Gilenya initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with Gilenya should not be initiated in patients who are concurrently treated with these substances. In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks. If treatment with Gilenya is considered, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products prior to initiation of treatment. If the heart-rate-lowering medication cannot be stopped, cardiologist's advice should be sought to determine appropriate first dose monitoring, at least overnight extended monitoring is recommended. SmPC also states that 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 treatment initiation should apply.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		Additional risk minimization activity: Educational material for physicians and patients. A physician's checklist prior to prescribing and a patient reminder card will describe this transient pharmacodynamic effect and will highlight that during initiation of Gilenya therapy for all patients starting treatment, the following monitoring should be applied: ECG and blood pressure measurement prior to and 6 hours after the first dose and Blood pressure and heart rate measurement every hour for 6 hours. Continuous (real time) ECG monitoring is recommended during the 6-hour period. If patient's heart rate at the end of the 6-hour period is the lowest following first dose administration, the monitoring should be extended by at least 2 hours and until the heart rate increases. Extended monitoring, including at least overnight monitoring, is recommended in those patients who experience any of the following at the 6-hour time point after the first dose: heart rate < 45 beats per minute QTc interval ≥500 msec. new onset second degree or higher AV block Occurrence at any time of third degree atrioventricular block should also lead to extended monitoring
Hypertension	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying	Risk addressed in SmPC sections 4.4 and 4.8 and derived local labels: Blood pressure should be regularly monitored during treatment with Gilenya. 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

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy. Proposed substudy: currently being planned with the primary objective of estimating the incidence of cardiovascular adverse events in fingolimod treated patients who experienced a bradyarrhythmic event that led to extended monitoring during treatment initiation of fingolimod vs. patients treated with a DMT.	treated with Gilenya. In MS clinical trials, patients treated with fingolimod 0.5 mg had an average increase of approximately 3 mmHg in systolic pressure, and approximately 1 mmHg 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 6.1% of patients on fingolimod 0.5 mg and in 3.8% of patients on placebo. In the post-marketing setting, 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 Gilenya
Liver transaminase elevation	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy.	Risk addressed in SmPC sections 4.2, 4.4 and 4.8 and derived local labels: SmPc states that during clinical trials, elevations 3-fold the upper limit of normal (ULN) or greater in liver transaminases occurred in 8% of patients treated with fingolimod 0.5 mg compared to 2% of placebo patients. Elevations 5-fold the ULN occurred in 2% of patients on fingolimod and 1% of patients on placebo. In clinical trials, fingolimod was discontinued if the elevation exceeded 5 times the ULN. Recurrence of liver transaminase elevations occurred with rechallenge in some patients, supporting a relationship to fingolimod. 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. Gilenya has not been studied in patients with severe pre-existing hepatic injury (Child-Pugh class C) and must not be used in these patients (see section 4.3).

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		Due to the immunosuppressive properties of fingolimod, 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 Gilenya. In the absence of clinical symptoms, liver transaminases levels should be monitored at months 1, 3, 6, 9 and 12 on therapy and periodically thereafter. If liver transaminases riseabove 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 Gilenya should be interrupted and only re-commenced once liver transaminases values have normalized. 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 (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 Gilenya, caution in the use of Gilenya should be exercised in patients with a history of significant liver disease. Additional risk minimization activity: Educational material for physicians and patients. A physician's checklist prior to prescribing and a

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		patient reminder card will inform on the need for liver function tests prior to initiation and during Gilenya therapy.
Macular edema	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D 2316: 4-month, open-label, multi-center study to explore tolerability and safety and health outcomes of FTY720 in patients with relapsing forms of MS Study FTY7202403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy.	Risk addressed in SmPC sections 4.4 and 4.8 and derived local labels: Macular edema with or without visual symptoms has been reported in 0.4% of patients treated with fingolimod 0.5 mg, 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 edema. 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 ophthalmological evaluation prior to initiating therapy and have follow-up evaluations while receiving therapy. Continuation of Gilenya in patients with macular edema has not been evaluated. It is recommended that Gilenya be discontinued if a patient develops macular edema. A decision on whether or not Gilenya therapy should be re-initiated after resolution of macular edema needs to take into account the potential benefits and risks for the individual patient. Additional risk minimization activity: Educational material for physicians and patients. A physician's checklist prior to prescribing and a patient reminder card will inform on the risk of macular edema. Through this activity physicians and patients will be made aware of potential vision deterioration on fingolimod and the need for regular

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		vision checks.
Infections	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy.	Risk addressed in SmPC sections 4.4 and 4.8 and derived local labels: SmPC state that the immune system effects of fingolimod therapy may increase the risk of infections. The SmPC will also state that two fatal herpetic infections occurred in patients on the 1.25 mg dose. As could be considered for any immune modulating drug, before initiating fingolimod 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 fingolimod, following which initiation of treatment with fingolimod should be postponed for 1 month to allow full effect of vaccination to occur. SmPC recommendation to avoid the administration of live or live attenuated vaccines while patients are taking fingolimod and for 2 months after discontinuation. SmPC states that before initiating treatment with fingolimod, a recent complete blood count (CBC) (i.e. within 6 months) should be available. Assessments of CBC are also recommended periodically during treatment, and in case of signs of infections. Absolute lymphocyte count <0.2 x10^9/L, if confirmed, should lead to treatment interruption, until recovery, because in clinical studies, fingolimod treatment was interrupted in patients with absolute lymphocyte count <0.2 x10^9/L. Additional risk minimization activity: Educational material for physicians and patients. A physician's checklist prior to prescribing and a patient reminder card will inform on the risk of increased infection with fingolimod, and the need to immediately report signs and symptoms of infections to the prescriber.
Leucopenia and lymphopenia	Routine pharmacovigilance,	Risk addressed in SmPC Section

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	including cumulative review in PSUR.	4.4, 5.1 and CDS Section 6 and derived local labels: SmPC Section 4.4 and CDS Section 6 state that a core pharmacodynamic effect of Gilenya is 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. Further information relating to this risk is provided under infections above.
Reproductive toxicity	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY7202404: The Multinational Pregnancy Fingolimod Exposure Registry in Multiple Sclerosis to prospectively collect outcome data on the babies born to women treated with fingolimodand compare it to reference data from general surveillance systems. With the establishment of a Fingolimod Pregnancy Exposure Registry, Novartis seeks to obtain comprehensive data on the outcome of any pregnancies that occur during the use of fingolimod.	Risk addressed in SmPC section 4.6 and derived local labels: SmPC recommendation for females of child-bearing potential to practice effective contraception during treatment with fingolimod and for 2 months post-drug discontinuation to cover the period of elimination of the drug. SmPC also states that before initiation of treatment in women of childbearing potential a negative pregnancy test result needs to be available. If a woman becomes pregnant while taking Gilenya, discontinuation of Gilenya is recommended. Additional risk minimization activity: Educational material for physicians and patients. A physician's checklist prior to prescribing and a patient reminder card will outline the known teratogenic risks with fingolimod, the need for a negative pregnancy test before initiation of treatment in women of childbearing potential,and explain the importance of avoiding pregnancy when undergoing treatment with fingolimod.
Bronchoconstriction	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy	SmPC section 4.4 states that minor dose-dependent reductions in values for forced expiratory volume (FEV_1) and diffusion capacity for carbon monoxide (D_LCO) were observed with Gilenya treatment starting at Month 1 and remaining stable thereafter. Fingolimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease. Physicians are properly

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy.	informed of this risk.
Important potential risks		
Skin cancer	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy.	Risk is not presented in the SmPC.
Other malignant neoplasms	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy. Study FTY720D2399: Long-term study in patients who participated in the fingolimod clinical development program. Targeted follow-up of all spontaneous reports of non-cutaneous malignancies.	SmPC section 5.3 states that fingolimod increased the risk of developing lymphomas in animal studies. SmPC section 4.8 states that three cases of lymphoma (cutaneous T-cell lymphoproliferative disorders or diffuse B-cell lymphoma including one fatal EBV positive B-cell lymphoma) have been reported in a population of more than 4,000 patients (approximately 10,000 patient-years) exposed to fingolimod at, or above, the recommended dose of 0.5 mg, during the clinical program in multiple sclerosis. This incidence of 3 in 10,000 patient years (95% CI: 0.6-8.8 per 10,000 patient years) compares to a background incidence of 1.9 in 10,000 patient years in the general population. Physicians are properly informed of this risk.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Posterior Reversible Encephalopathy Syndrome (PRES) and acute disseminated encephalomyelitis-like (ADEM-like) events	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy.	SmPC section 4.8 states that rare events involving the nervous system which occurred in patients treated with fingolimod at higher doses (1.25 or 5.0 mg) including posterior reversible encephalopathy syndrome. Neurological atypical disorders have also been reported, such as ADEM-like events. Physicians are properly informed of this risk.
Thromboembolic events	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy. Proposed substudy: currently being planned with the primary objective of estimating the incidence of cardiovascular adverse events in fingolimod treated patients who experienced a bradyarrhythmic event that led to extended monitoring during treatment initiation of fingolimod vs. patients treated with a DMT. Targeted follow-up of all serious spontaneous reports of stroke and ischemic cardiac events using two targeted checklists.	SmPC section 4.8 includes information on the small number of cases with possible thromboembolic events (including cerebrovascular and peripheral vascular events) observed in the fingolimod clinical trial program.
QT interval prolongation	Routine pharmacovigilance, including cumulative review in	SmPC Sections 4.4 and 5.1 include results of the thorough QT study

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy. Proposed substudy: currently being planned with the primary objective of estimating the incidence of cardiovascular adverse events in fingolimod treated patients who experienced a bradyarrhythmic event that led to extended monitoring during treatment initiation of fingolimod vs. patients treated with a DMT.	which showed a prolongation of mean corrected QT interval, with the upper limit of the 90% CI ≤13.0 msec on fingolimod treatment. Section 4.4 states that if, after 6 hours, QTc interval ≥ 500 msec extended monitoring (at least overnight monitoring), should be performed, and until the findings have resolved Gilenya should not be used in patients with significant QT prolongation (QTc>470msec (female) or >450msec (male)). Medicinal products that may prolong QTc interval are best avoided in patients with relevant risk factors, for example, hypokalaemia or congenital QT prolongation
Convulsions	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy.	Risk is not presented in the SmPC.
Progressive multifocal leukoencephalopathy (PML)	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started	Risk is not presented in the SmPC.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy.	
Reactivation of chronic viral infections	Routine pharmacovigilance, including cumulative review in PSUR.	Risk is addressed in SmPC Section 4.4, 4.8 and CDS Section 6 and derived local labels. See section on Infections above.
Off-label use	Routine pharmacovigilance, including cumulative review in PSUR.	Risk is not presented in the SmPC.
Pulmonary edema	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy.	Risk is not presented in the SmPC.
Decreased renal function	Routine pharmacovigilance, including cumulative review in PSUR.	According to SmPC section 4.2, fingolimod has not been studied in patients with renal impairment in the MS pivotal studies. Based on clinical pharmacology studies, no dose adjustments are needed in patients with mild to severe renal impairment.
Potential interactions		
Ketoconazole	Routine pharmacovigilance, including review in PSUR.	According to SmPC section 4.5, co-administration of fingolimod with ketoconazole resulted in a 1.7-fold increase in fingolimod and fingolimod phosphate exposure (AUC). Caution should be

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		exercised with substances that may inhibit CYP3A4 (protease inhibitors, azole antifungals, some macrolides such as clarithromycin or telithromycin).
Atenolol	Routine pharmacovigilance, including review in PSUR.	According to SmPC section 4.4 Experience with Gilenya is limited in patients receiving concurrent therapy with 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, anticholinesteratic agents or pilocarpine). Since the initiation of Gilenya treatment is also associated with slowing of the heart rate (see, Bradyarrhythmia), concomitant use of these substances during Gilenya initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate treatment with Gilenya should not be initiated in patients who are concurrently treated with these substances In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks. If treatment with Gilenya is considered, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products prior to initiation of treatment. If the heart-rate-lowering medication cannot be stopped, cardiologist's advice should be sought to determine appropriate first dose monitoring, at least overnight extended monitoring is recommended According to section 4.5 of the SmPC Fingolimod 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 treatment initiation, an effect not seen with diltiazem. Treatment with Gilenya should not be initiated in patients receiving beta blockers, or other

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		substances which may decrease heart rate, such as class Ia and III antiarrhythmics, calcium channel blockers (such as, verapamil, diltiazem or ivabradine), digoxin, anticholinesteratic agents or pilocarpine because of the potential additive effects on heart rate If treatment with Gilenya is considered in such patients, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products or appropriate monitoring for treatment initiation, at least overnight monitoring is recommended, if the heart-rate-lowering medication cannot be stopped.
Important missing information		
Elderly patients	Routine pharmacovigilance, including cumulative review in PSUR.	According to SmPC Section 4.2, fingolimod should be used with caution in patients aged 65 years and over due to insufficient data on safety and efficacy.
Pediatric patients	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2311: EMEA pediatric investigation plan (EMEA-000087-PIP01-07): Open-label, randomized, multicenter, multiple dose, active controlled (interferon beta-1a), parallel group 2-year trial to evaluate pharmacokinetics, safety and efficacy of fingolimod using blinded MRI assessment in patients with MS from 10 to less than 18 years of age followed by a long-term extension.	The safety and efficacy of fingolimod in children aged 0 to 18 years have not yet been established. Currently available data are described in section 5.2 of SmPC but no recommendation on a posology can be made.
Pregnant and lactating women	Routine pharmacovigilance, including review in PSUR. Study FTY7202404: The Multinational Pregnancy Fingolimod Exposure Registry in Multiple Sclerosis to prospectively collect outcome data on the babies born to women treated with fingolimod.	According to SmPC Section 4.6, before initiation of fingolimod treatment, women of childbearing potential should be counseled on the potential for serious risk to the fetus and the need for effective contraception during treatment with fingolimod. Since it takes approximately two months to eliminate fingolimod from the body on stopping treatment (see section 4.4), the potential risk to the fetus may persist and contraception should be continued during that period. It should be confirmed that a woman is not pregnant at the time

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		of initiation of treatment. While on treatment, women should not become pregnant and active contraception is recommended. If a woman becomes pregnant while taking Gilenya, discontinuation of Gilenya is recommended. 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 fingolimod should not breast feed. Educational material for physicians and patients. A physician's checklist prior to prescribing and a patient reminder card will outline the known teratogenic risks with fingolimod, the need for a negative pregnancy test before initiation of treatment in women of childbearing potential,and explain the importance of avoiding pregnancy when undergoing treatment with fingolimod.
Patients with diabetes mellitus	Routine pharmacovigilance, including cumulative review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy.	Recommendation in the SmPC Section 4.4 that patients with diabetes mellitus undergo an ophthalmologic evaluation prior to initiating fingolimod therapy and have follow-up evaluations while receiving fingolimod therapy. According to the SmPC section 4.2, fingolimod has not been studied in MS patients with concomitant diabetes mellitus. It should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular edema.
Patients with cardiovascular conditions	Routine pharmacovigilance, including review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying	Recommendation in the SmPC Section 4.4 that due to the risk of serious rhythm disturbances, Gilenya should not be used in patients with second degree Mobitz type II or higher AV block, sick-sinus syndrome, sino-atrial heart block, a history of symptomatic bradycardia or recurrent syncope, or in patients with significant QT

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy. Proposed substudy: currently being planned with the primary objective of estimating the incidence of cardiovascular adverse events in fingolimod treated patients who experienced a bradyarrhythmic event that led to extended monitoring during treatment initiation of fingolimod vs. patients treated with a DMT. Targeted follow-up of all serious spontaneous reports of stroke and ischemic cardiac events using two targeted checklists.	prolongation (QTc >470 msec (females) or >450 msec (males)). Since significant bradycardia may be poorly tolerated in patients with known ischemic heart disease, (including angina pectoris), cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension, or severe untreated sleep apnoea, Gilenya should not be used in these patients. In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks. If treatment 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.
Long-term risk of cardiovascular morbidity/mortality	Routine pharmacovigilance, including review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy. Proposed substudy: currently being planned with the primary objective of estimating the incidence of cardiovascular adverse events in fingolimod treated patients who experienced a bradyarrhythmic event that led to extended monitoring during treatment initiation of fingolimod vs. patients treated with a DMT. Targeted follow-up of all serious spontaneous reports of stroke and ischemic cardiac events using two	Risk is not presented in the SmPC

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	targeted checklists.	
Long-term risk of malignant neoplasms	Routine pharmacovigilance, including review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy.Study FTY720D2399: Long-term study in patients who participated in the fingolimod clinical development program	According to SmPC Section 4.8, cases of lymphoma (cutaneous T-cell lymphoproliferative disorders or diffuse B-cell lymphoma) have been reported in MS patients receiving fingolimod at, or above, the recommended dose of 0.5 mg. Based on the small numbers of cases and short duration of exposure, the relationship to Gilenya remains uncertain.
Unexplained death	Routine pharmacovigilance, including review in PSUR. Study FTY720D2403: Long term, prospective, observational, multinational, parallel cohort study monitoring safety in patients with multiple sclerosis newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease modifying therapy Study FTY720D2406: Long term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease modifying therapy. Proposed substudy: currently being planned with the primary objective of estimating the incidence of cardiovascular adverse events in fingolimod treated patients who experienced a bradyarrhythmic event that led to extended monitoring during treatment initiation of fingolimod vs. patients treated with a DMT. Targeted follow-up of all serious spontaneous reports using a	According to SmPC Section 4.8, in the post-marketing setting, isolated delayed onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. These cases have been confounded by concomitant medicinal products and/or pre-existing disease. The relationship of such events to Gilenya is uncertain.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	targeted checklist.	

The following additional risk minimisation activities were required:

- Direct Healthcare Professional Communication
- Revised Patient reminder Card
- Revised Physician Checklist

In addition, the below condition to the Marketing authorisation is needed, to investigate further some of the safety concerns:

Description	Due date
Conduct of a prospective cohort study assessing the incidence of cardiovascular adverse events in patients starting GILENYA treatment for relapsing remitting multiple sclerosis based on a CHMP approved protocol.	Final study report by 15 December 2020

In addition study FTY720D2121, a double blind, placebo controlled, parallel group study to investigate two different dose-titration regimens of fingolimod on the negative chronotropic effect of fingolimod in healthy subjects which is already started has been added in the risk Management plan

Furthermore, the CHMP considered that the MAH should take the following minor points into consideration when an update of the Risk management Plan is submitted:

In Annex 8 the MAH has put key messages of the conditions, however the actual components of the educational materials (patient reminder card and physician checklist) with relevant changes addressing the outcome of this procedure is required. The MAH committed provide those materials with next update of RMP.

For study D2406, the timing of recruitment, inclusion criteria and sample size should be further reviewed and assessed by the CHMP. The MAH has committed to submit a revision by 31 May 2012.

1.1. Product information

The CHMP recommended amendments to be introduced in the summary of product characteristics (SPC), Annex II and package leaflet. Within the summary of product characteristics sections 4.4, 4.5, 4.8, 4.9 and 5.1 were updated with the safety information following the CHMP recommendations (see attachment to this report).

1.2. Direct Healthcare Professional Communication (DHPC)

As part of this procedure, the MAH and the CHMP agreed the wording of two 'Direct Healthcare Professional Communication' designed to inform prescribers of the Gilenya (see relevant attachments to this Report).

Following the CHMP recommendations, the MAH provided an action plan for the DHPC (see attachment to this report), to be sent to relevant health care professionals.

2. Overall conclusion and benefit / risk balance

In conclusion the CHMP reviewed all safety data available from clinical trial studies, alongside with all data from post-marketing data. These suggested an increased risk of adverse cardiovascular outcomes during the first 6 hours of administration of the first dose of fingolimod and especially bradyarrhythmia. Patients at risk have been identified as patients with history of cardiovascular and cerebrovascular events, as well patients receiving heart rate lowering agents such as beta-blockers and calcium channel blockers. In addition the incidents of hypertension are increasing with the administration of fingolimod. So the CHMP issued the following recommendations.

All patients who start treatment with Gilenya should have an ECG and blood pressure measurement performed prior to and 6 hours after the first dose of Gilenya and 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 was recommended. Moreover, patients should be monitored until any observed symptoms seize to exist.

Due to the risk of serious rhythm disturbances, the CHMP agreed that Gilenya should not be used in patients at risk. These include patients with second degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial heart block, in patients with a history of symptomatic bradycardia or recurrent syncope, or patients with significant QT prolongation.

The CHMP considered that concomitant use of fingolimod with substances such as beta blockers, heart rate lowering calcium channel blockers may be associated with severe bradycardia and heart block. Therefore the CHMP recommended that treatment should not be initiated in patients who are concurrently treated with these substances. If treatment is considered in such patients, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products or appropriate monitoring for treatment initiation (at least overnight) if the heart-rate-lowering medication cannot be stopped.

As fingolimod has been shown to provoke hypertension the CHMP concluded that Gilenya should not be used in patients of uncontrolled hypertension and until the hypertension is brought under control.

The CHMP endorsed additional risk minimisation activities including a Direct Healthcare Professional Communication (DHPC). A previous communication was sent in January 2012 at the start of the procedure giving some preliminary recommendations to prescribers. In addition, the educational material to prescribers and patients was updated.

The CHMP also agreed that a prospective cohort study assessing the incidence of cardiovascular adverse events in patients starting Gilenya treatment need to be conducted.

Benefit-risk balance

In view of the above data the CHMP agreed that the benefit-risk balance of Gilenya in the treatment of relapsing remitting multiple sclerosis remains positive under normal conditions of use, subject to the conditions, warnings, other changes to the product information, additional pharmacovigilance activities and risk minimisation measures agreed.

Therefore the CHMP, recommended the variation to the terms of the marketing authorisation for which the revised product Information is set out in Annex III of the opinion.

The scientific conclusions and the grounds for the amendment of the SmPC, Annex II, and package leaflet and the Annex under Article 127a are set out in Annex IV of the opinion.

The conditions affecting the marketing authorisation, as referred to in Article 32(4) of Directive 2001/83/EC as amended, are set out in Annex IV of the opinion.

3. Recommendations

Update of sections 4.4, 4.5, 4.8 and 4.9 of the SmPC in order to add a warning update the safety information regarding the cardiovascular safety of Gilenya following the first dose administration. The Package Leaflet is updated in accordance.

3.1. Conditions and requirements of the marketing authorisation

Risk management system

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3.2 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

The CHMP agreed that updated educational material needs to be distributed by the MAH to insure the safe administration of Gilenya. The updated information pack should contain

- The Summary of Product Characteristics
- Physician's checklist prior to prescribing Gilenya
- Information about the Fingolimod Pregnancy Exposure Registry
- Patient reminder cards

More detailed description is reported in the following list:

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

The Member States shall agree the final educational material with the Marketing Authorisation Holder (MAH) prior to launch in their territory.

The Member States shall ensure that, at launch and after launch, the MAH provides all physicians who intend to prescribe GILENYA with an updated physician information pack containing the following elements:

- The Summary of Product Characteristics
- Physician's checklist prior to prescribing GILENYA
- Information about the Fingolimod Pregnancy Exposure Registry
- Patient reminder cards

The physician's checklist shall contain the following key messages:

o Monitoring requirements at treatment initiation

Before first dose

- o Perform baseline ECG prior to the first dose of GILENYA (or when the last dose of GILENYA was more than two weeks previously).
- o Perform blood pressure measurement prior to the first dose of GILENYA (or when the last dose of GILENYA was more than two weeks previously).

- Perform a liver function test prior to treatment initiation.
- Arrange ophthalmologic assessment prior to initiation with GILENYA in patients with diabetes mellitus or with a history of uveitis.

Until 6 hours after first dose (or if the last dose of GILENYA was more than two weeks previously)

- Monitor the patient for 6 hours after the first dose of GILENYA has been administered for signs and symptoms of bradycardia, including hourly pulse and blood pressure checks. Continuous (real time) ECG monitoring is recommended.
- Perform an ECG at the end of the 6 hour monitoring period.

>6 to 8 hours after first dose (or if the last dose of GILENYA was more than two weeks previously)

- If at the 6 hour time point, the heart rate is at the lowest value following the first dose, extend heart rate monitoring for at least 2 more hours and until the heart rate increases again.

If a patient requires pharmacologic intervention during monitoring at treatment initiation overnight monitoring in a medical facility should be instituted.

- Recommendation for overnight monitoring after the first dose (or if the last dose of GILENYA was more than two weeks previously)

  Extend heart rate monitoring for at least overnight in a medical facility and until resolution of findings in patients
  - Requiring pharmacologic intervention during monitoring at treatment initiation
  - With 3rd degree AV block occurring at any time
  - Where at the 6 hour time point:
    - Heart rate < 45 bpm
    - New onset 2nd degree or higher AV block
    - QTc interval ≥ 500 msec

- That GILENYA is not recommended in patients with:
  - 2nd degree Mobitz Type II or higher AV block
  - Sick-sinus syndrome
  - Sino-atrial heart block
  - QTc prolongation >470 msec (females) or >450 msec (males)
  - Ischaemic cardiac disease including angina pectoris
  - Cerebrovascular disease
  - History of myocardial infarction
  - Congestive heart failure
  - History of cardiac arrest
  - Severe sleep apnea
  - History of symptomatic bradycardia
  - History of recurrent syncope
  - Uncontrolled hypertension.

  If GILENYA treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to determine appropriate monitoring, at least overnight extended monitoring is recommended.
- GILENYA is not recommended in patients taking concomitantly Class IA or Class III anti-arrhythmic medicines.
- GILENYA is not recommended in patients concomitantly taking medicines which are known to decrease the heart rate. If GILENYA treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to switch to non-heart rate

lowering therapy or, if not possible to determine appropriate monitoring. At least overnight extended monitoring is recommended.

- GILENYA reduces peripheral blood lymphocyte counts. There is a need to check the patient's peripheral lymphocyte count (CBC) prior to initiation and to monitor during treatment with GILENYA.
- GILENYA may increase the risk of infections. Treatment initiation in patients with severe active infection should be delayed until the infection is resolved. Suspension of treatment during serious infections should be considered. Concomitant treatment with immunosuppressants or immune modulating medicines should be avoided.
- The need to instruct patients to report signs and symptoms of infections immediately to their prescriber during and for up to two months after treatment with GILENYA.
- Specific recommendations regarding vaccination for patients initiating or currently on GILENYA treatment.
- The need for a full ophthalmologic assessment 3-4 months after starting GILENYA therapy for the early detection of visual impairment due to drug-induced macular edema.
- The need for ophthalmologic assessment during treatment with GILENYA in patients with diabetes mellitus or with a history of uveitis.
- The teratogenic risk of GILENYA: the importance of avoiding pregnancy when undergoing treatment with GILENYA and the need for a negative pregnancy test result prior to treatment initiation. This should be repeated at suitable intervals.
- The need to advise women of child-bearing potential on the serious risk to the foetus and to need to practice effective contraception during treatment and for at least two months following discontinuation of treatment with GILENYA.
- The need for a liver function monitoring at months 1, 3, 6, 9 and 12 during GILENYA therapy and periodically thereafter.
- The need to provide patients with the patient reminder card.

The patient reminder card shall contain the following key messages:

- That they will have a baseline ECG and blood pressure measurement prior to the first dose of GILENYA (or when the last dose of GILENYA has been administered more than two weeks ago).
- That their heart rate will need to be monitored for 6 or more hours after the first dose of GILENYA (or when the last dose of GILENYA has been administered more than two weeks ago) including hourly pulse and blood pressure checks. Patients may be monitored with a continuous ECG during the first 6 hours. They will need an ECG at 6 hours and in some circumstances monitoring may involve an overnight stay.
- The need to report immediately symptoms indicating low heart rate (such as dizziness, vertigo, nausea or palpitations) after the first dose of GILENYA.
- GILENYA is not recommended in patients with cardiac disease or those taking medicines concomitantly known to decrease heart rate and they should tell any doctor they see that they are being treated with GILENYA.
- The signs and symptoms of infection and the need to report these immediately to the prescriber during and up to two months after treatment with GILENYA.
- The need to report any symptoms of visual impairment immediately to the prescriber during and for up to two months after treatment finishes with GILENYA.
- That GILENYA is teratogenic so women with childbearing potential must:
    - Have a negative pregnancy test
    - Be using effective contraception during and for at least two months following discontinuation of treatment with GILENYA.
    - Report any (intended or unintended) pregnancy during and two months following discontinuation of treatment with GILENYA immediately to the prescriber.

o The need for a liver function test prior to treatment initiation and for liver function monitoring at months 1, 3, 6, 9 and 12 during GILENYA therapy and periodically thereafter.

4. Grounds for the recommendation

Whereas

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Gilenya initiated by the European Commission.
- The Committee reviewed the available safety data from clinical trials and post-marketing data on the cardiovascular adverse events reported and in particular during the 24 hours after first dose administration of Gilenya.
- In view of the available data the Committee concluded that serious cases of bradyarrhythmia and hypertension have been reported with fingolimod. These occur in particular by 6 hours after the first dose administration of Gilenya.
- The Committee therefore recommended that all patients should have an ECG and blood pressure measurement performed at baseline prior to the first dose of Gilenya. The committee agreed that Gilenya should not be used in patients at risk of cardiovascular disease and as use of beta blockers and calcium channel blockers during treatment initiation may be associated with severe bradycardia and heart block, Gilenya should not be initiated in patients who are concurrently treated with these substances. Furthermore, if treatment is considered in all these at risk patients, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring (at least overnight) for treatment initiation. These recommendations are reflected in the updated summary of product characteristics.
- The Committee is of the opinion that Gilenya should not be used in patients of uncontrolled hypertension until the hypertension is brought under control.
- The Committee, as a consequence, concluded that the benefit-risk balance of Gilenya in the treatment of highly active relapsing remitting multiple sclerosis remains positive under normal conditions of use, subject to the conditions, warnings, changes to the product information, additional pharmacovigilance activities and risk minimisation measures agreed.

The CHMP has therefore recommended the variation to the terms of the marketing authorisation for Gilenya in accordance to the Product Information set out in annexes I, II and IIIB and update of Annex related to Article 127a.