Gilenya

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0090/G	This was an application for a group of variations. Grouped application comprising two variations as follows: Type II (C.I.3.b) - Update of section 4.3 of the SmPC in order to add suspected or confirmed progressive	14/11/2024	16/12/2024	SmPC, Annex II and PL	The product information is updated to add suspected or confirmed PML as a contraindication, to add IRIS as an ADR with frequency not known and to amend a warning on PML and add a warning on IRIS. For more information, please refer to the Summary of Product Characteristics.

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	multifocal leukoencephalopathy (PML) as a new contraindication; update of section 4.4 of the SmPC to amend an existing warning on PML and to add a new warning on immune reconstitution inflammatory syndrome (IRIS) and update of section 4.8 of the SmPC in order to add IRIS as ADR with frequency not know. The educational materials are updated on information about IRIS and also updated to improve the general readability and better address key messages and recommendations for healthcare professionals and for patients following the assessment of procedure PSUSA/00001393/202302. The Package Leaflet and Annex II are updated accordingly. The RMP version 20.2 has also been agreed. Type IA (A.6) - To change the ATC Code of Fingolimod from L04AA27 to L04AE01. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH A.6 - Administrative change - Change in ATC Code/ATC Vet Code				
IA/0096/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where	15/11/2024	n/a		

	batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
IAIN/0097/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP -	14/11/2024	16/12/2024	Annex II and PL	

	Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
IA/0095/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)	19/06/2024	n/a		
IA/0094/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	14/06/2024	n/a		

IA/0093/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	14/06/2024	n/a		
IAIN/0091	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	04/04/2024	n/a		
IAIN/0089	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	04/04/2024	n/a		
IA/0087	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	19/02/2024	n/a		
IB/0086	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	09/11/2023	n/a		
PSUSA/1393/202302	Periodic Safety Update EU Single assessment - fingolimod	26/10/2023	n/a		PRAC Recommendation - maintenance
IA/0085/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	26/09/2023	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				
IAIN/0084/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	14/09/2023	19/04/2024	Annex II and PL	
IB/0081/G	This was an application for a group of variations. B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	09/05/2023	19/04/2024	SmPC, Annex II and Labelling	

	B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.III.1.b.2 - Submission of a new/updated or				

	deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.II.a.z - Change in description and composition of the Finished Product - Other variation B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a				

	new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits				
IAIN/0082	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	27/02/2023	n/a		
IA/0080	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	02/12/2022	23/02/2023	SmPC, Labelling and PL	
IA/0079	A.7 - Administrative change - Deletion of manufacturing sites	03/10/2022	n/a		
IA/0078	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	01/08/2022	n/a		
IB/0077/G	This was an application for a group of variations. B.II.b.4.b - Change in the batch size (including batch	29/07/2022	23/02/2023	Annex II and PL	

	size ranges) of the finished product - Downscaling down to 10-fold B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the				

	finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch				

	control/testing takes place B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site				

IB/0075/G	This was an application for a group of variations. B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	14/07/2022	n/a		

	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
IG/1521	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	23/06/2022	n/a		
IB/0074	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	22/03/2022	23/02/2023	SmPC	PI is updated to reflect extension of the shelf life of the finished product Gilenya 0.25 mg Capsule, hard as packed for sale from 18 months to 24 months with storage condition `Do not store above 25 °C' for countries in Climatic Zone I & II.
IA/0073/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	31/01/2022	n/a		

	procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits				
PSUSA/1393/ 202102	Periodic Safety Update EU Single assessment - fingolimod	30/09/2021	n/a		PRAC Recommendation - maintenance
IA/0072	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	09/09/2021	n/a		
II/0070/G	This was an application for a group of variations. Submission of the non-interventional final study	08/07/2021	27/01/2022	SmPC, Annex II and PL	

	report D2403 (long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with multiple sclerosis newly started on fingolimod once daily or treated with another approved disease-modifying therapy). Submission of the non-interventional final study report D2406/D2409 (long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS newly initiated on fingolimod once daily or treated with another approved disease-modifying therapy (including cardiac sub-study D2409)). Consequently, the Annex IID is updated to remove the obligation to perform the PASS D2409. The RMP v 19.1 has been agreed. In addition, the MAH took the opportunity to implement some minor editorial changes and to update the UK (Northern Ireland) local representative details in the PL. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IA/0069	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished	22/02/2021	n/a		

	product formulation - Change that does not affect the product information				
IB/0068	C.z - Safety, Efficacy, Pharmacovigilance changes - Other variation	07/01/2021	27/01/2022	Annex II	
PSUSA/1393/202002	Periodic Safety Update EU Single assessment - fingolimod	15/10/2020	14/12/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1393/202002.
IA/0067	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	07/12/2020	n/a		
R/0063	Renewal of the marketing authorisation.	17/09/2020	16/11/2020	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Gilenya in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/0065	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	07/08/2020	16/11/2020	Annex II	
IB/0066	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	31/07/2020	n/a		
IAIN/0064	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	15/07/2020	n/a		

IA/0061	B.I.c.1.z - Change in immediate packaging of the AS - Other variation	17/04/2020	n/a		
IA/0060/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability -	27/03/2020	n/a		

	Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability -				

	Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
PSUSA/1393/201902	Periodic Safety Update EU Single assessment - fingolimod	17/10/2019	16/12/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1393/201902.
IAIN/0059/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	24/10/2019	n/a		

IB/0058/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	16/09/2019	n/a		
II/0053	To update section 4.4 (subsection 'Return of disease activity (rebound)' and subsection 'Stopping therapy') to add information to prescribers on the timing of reported events and further recommendations on monitoring of patients, section 4.6 to add a warning for women stopping treatment for the purpose of becoming pregnant and for pregnant women and section 4.8 to add a new adverse reaction 'Severe exacerbation of disease after Gilenya discontinuation' with frequency 'Not known'. Additional information is included regarding the potential benefit of Gilenya use in pregnant women and women of child-bearing potential (WCBP) not using effective contraception regarding its reproductive toxicity in sections 4.3 to add contraindication regarding pregnant women and WCBP not using effective contraception, 4.4 to add a warning, with a cross reference to the contraindication and 4.6 to add information regarding the contraindication (the 2 fold increase risk of malformation and the malformations types; a	25/07/2019	03/09/2019	SmPC, Annex II and PL	The MAH provided a review of information from the published literature (Vermersch et al (2017)), including epidemiological evaluation, the Novartis safety database, and clinical studies (FREEDOMS/FTY720D2301 and FREEDOMS II/FTY720D2309) covering at least 3 months after treatment withdrawal to support a labelling update regarding rebound effect (in sections 4.4, 4.6 and 4.8). This has generally been observed within 12 weeks after stopping fingolimod, but has also been reported up to 24 weeks after fingolimod discontinuation recommending the patient monitoring if treatment discontinuation is deemed necessary. Furthermore, post marketing data was also provided to support changes related to the LEG 037 procedure concerning the increased risk of major congenital malformations and contraindication of Gilenya use in pregnant women and women of child-bearing potential, not using effective contraception regarding its reproductive toxicity. As a result SmPC sections 4.3, 4.4 and 4.6 have been updated to include contraindication regarding pregnant women and WCBP not using effective

	cross-reference to the educational materials and a reference that Gilenya must be stopped if a women becomes pregnant, medical advice should be given regarding the risk to the foetus and the need for ultrasonography examinations). The Package Leaflet is updated accordingly. The updated RMP version 16.1 has also been submitted to remove the "PRIM" (Gilenya Pregnancy outcomes Intensive Monitoring) and to introduce amendments to the protocol of Study D2404 and update of the educational materials to reflect the contraindication (update of physician's checklist, rename the Patient / Parent / Caregiver card to a Patient / Parent / Caregiver guide with update of the key messages, addition of measures to prevent pregnancy and introduction of a new Pregnancy-specific patient reminder card). A DHPC and Communication plan was agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				contraception.
IG/1100	A.7 - Administrative change - Deletion of manufacturing sites	24/05/2019	n/a		
IG/1099	A.7 - Administrative change - Deletion of manufacturing sites	24/05/2019	n/a		
IB/0054/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of	23/05/2019	n/a		

	the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
IB/0052	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2018	03/09/2019	SmPC, Annex II, Labelling and PL	
PSUSA/1393/201802	Periodic Safety Update EU Single assessment - fingolimod	20/09/2018	22/11/2018	SmPC, Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1393/201802.
X/0044/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/09/2018	22/11/2018	SmPC, Annex II, Labelling and PL	
IA/0051	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	02/07/2018	22/11/2018	Annex II, Labelling and PL	
IA/0050/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new	27/06/2018	n/a		

	specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS				
II/0047	Submission of the CSR for Study D2399 (part 1), a long-term safety and tolerability study of fingolimod 0.5 mg/day in approximately 5000 patients with relapsing multiple sclerosis; the RMP is updated	17/05/2018	n/a		

	(version 14.1) to reflect the completion of the study. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
T/0048	Transfer of Marketing Authorisation	20/03/2018	23/04/2018	SmPC, Labelling and PL	
IB/0045	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/01/2018	23/04/2018	SmPC and PL	
IA/0046	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	18/12/2017	n/a		
PSUSA/1393/ 201702	Periodic Safety Update EU Single assessment - fingolimod	12/10/2017	08/12/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1393/201702.
IB/0043/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	10/10/2017	n/a		

	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting				

	material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
II/0040	Update of section 5.3 of the SmPC to include information about the dose correspondence between human and the species used for the preclinical tests of teratogenicity. RMP is updated (version 12.0). The MAH took the opportunity to make minor changes in sections 4.4, 4.5, 4.6 and 5.2 of the SmPC and also in Annex II. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/05/2017	08/12/2017	SmPC	Fingolimod was teratogenic in the rat when given at doses of 0.1 mg/kg or higher. Drug exposure in rats at this dose was similar to that in patients at the therapeutic dose (0.5 mg). The teratogenic potential in rabbits could not be fully assessed, however an increased embryo-foetal mortality was seen at doses of 1.5 mg/kg and higher, and a decrease in viable foetuses as well as foetal growth retardation was seen at 5 mg/kg. Drug exposure in rabbits at these doses was similar to that in patients. Before initiation of treatment in women of childbearing potential, a negative pregnancy test result needs to be available and counselling should be provided regarding the potential for serious risk to the foetus and the need for effective contraception during treatment with Gilenya.
II/0039	Update of sections 4.4 and 4.8 of the SmPC to add an approximate time of onset for multifocal leukoencephalopathy (PML) and for cryptococcal meningitis (CM) and to remove the term isolated from "isolated cases of CM". C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/01/2017	08/12/2017	SmPC	Section 4.4 of the SmPC has been amended to add the following detail to the existing warning on cryptococcal meningitis: "Cases of cryptococcal meningitis (a fungal infection) have been reported in the post-marketing setting after approximately 2 3 years of treatment, although an exact relationship with the duration of treatment is unknown." In addition, the existing warning on leukoencephalopathy (PML) has been updated with the following: "Cases of PML have occurred after approximately 2 3 years of monotherapy treatment without previous exposure to natalizumab, although an exact relationship with the duration of treatment is unknown. Additional PML cases

					have occurred in patients who had been treated previously with natalizumab, which has a known association with PML.”
PSUSA/1393/ 201602	Periodic Safety Update EU Single assessment - fingolimod	13/10/2016	08/12/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)’ for PSUSA/1393/201602.
IG/0712	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	03/08/2016	n/a		
II/0037	Update of sections 4.4 and 4.8 of the SmPC in order to amend the safety information to include additional warning and guidance on Progressive Multifocal Leukoencephalopathy (PML). The Package Leaflet is updated accordingly. In addition, the MAH took this opportunity to make corrections in the labelling. A new RMP version 11.0 was agreed during this procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/12/2015	25/01/2016	SmPC and PL	Case of Progressive Multifocal Leukoencephalopathy (PML) occurring in post marketing patients under Gilenya treatment. PML typically only occurs in patients who are immunocompromised. Before initiating treatment with fingolimod, a baseline Magnetic Resonance Imaging (MRI) should be available (usually within 3 months) as a reference. During routine MRI, physicians should pay attention to PML suggestive lesions. In case of PML is suspected, MRI should be performed immediately for diagnostic purposes and treatment with fingolimod should be suspended until PML has been excluded.
R/0036	Renewal of the marketing authorisation.	24/09/2015	23/11/2015		Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Gilenya continues to be favourable. However, since the first launch of the product, the following safety issues have been identified with Gilenya:

					bradyarrhythmia, PRES, lymphoma, periodicity of complete blood count (CBC), HPS, hypersensitivity following a bullous erythema multiform , PML, cryptococcal infections, opportunistic infections, BCC, urticarial, angioedema, Kaposi sarcoma, Tumefactive relapses, T-wave inversion, peripheral oedema, retinal disorders, RCVS, fatal cases including unexplained death and safety concerns after treatment by DMTs. These issues have led to updates of the SmPC and updates of the Pharmacovigilance Plan. Therefore, based upon the safety profile of Gilenya, which requires the submission of yearly PSURs, the CHMP was of the opinion that an additional five-year renewal on the basis of pharmacovigilance grounds was required.
PSUSA/1393/ 201502	Periodic Safety Update EU Single assessment - fingolimod	24/09/2015	19/11/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1393/201502.
II/0034	Extension of indication was amended to: Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy. As a consequence, section 4.1 of the SmPC is updated. In addition, the applicant took the opportunity to relocate documents from section 5.3.5.1 to 5.3.5.2." The variation proposed amendments to the Summary of Product Characteristics. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/09/2015	28/10/2015	SmPC	Please refer to scientific discussion in the published EPAR.

II/0032	Update of section 4.4 of the SmPC to include precautionary statements on cryptococcal meningitis and of section 4.8 of the SmPC to reflect cryptococcal infections, including isolated cases of cryptococcal meningitis. In addition, the Marketing authorisation holder took the opportunity to make a minor editorial change in section 4.5 of the SmPC to align with section 4.4 of the SmPC. The updated RMP version 9.0 has been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/05/2015	03/07/2015	SmPC and PL	Isolated cases of cryptococcal meningitis (a fungal infection) have been reported in the post-marketing setting. Patients with symptoms and signs consistent with cryptococcal meningitis (e.g. headache accompanied by mental changes such as confusion, hallucinations, and/or personality changes) should undergo prompt diagnostic evaluation. If cryptococcal meningitis is diagnosed, fingolimod should be suspended and appropriate treatment should be initiated. A multidisciplinary consultation (i.e. infectious disease specialist) should be undertaken if re-initiation of fingolimod is warranted.
IB/0033/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.a - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits for medicinal products subject to OCABR	18/05/2015	n/a		

IAIN/0031	A.1 - Administrative change - Change in the name and/or address of the MAH	02/03/2015	03/07/2015	SmPC, Labelling and PL	
IG/0484/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	12/11/2014	n/a		
PSUV/0029	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
II/0026/G	This was an application for a group of variations. Group of variations consisting of an update of sections 5.1 and 5.2 of the Summary of Product Characteristics to reflect additional data regarding the mechanism of action of fingolimod and two clinical studies regarding penetration of fingolimod in the CNS and its distribution in male semen, respectively. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	03/07/2015	SmPC	After the review of the submitted data, the CHMP recommended additional information related to the mechanism of action (ie redistribution of lymphocytes) and the distribution of fingolimod into the brain and male semen, respectively, in the SmPC, as follows: - Mechanism of action: Animal studies have shown that the redistribution of lymphocytes reduces the infiltration of pathogenic lymphocytes, including pro-inflammatory Th17 cells, into the CNS. - Distribution: A study in four healthy subjects who received a single intravenous dose of a radioiodolabelled analogue of fingolimod demonstrated that fingolimod penetrates into the brain. In a study in 13 male multiple sclerosis patients who received Gilenya 0.5 mg/day, the mean amount of fingolimod (and fingolimod phosphate) in seminal ejaculate, at steady-state, was approximately 10,000 times lower than the oral dose administered (0.5 mg).

PSUV/0027	Periodic Safety Update	25/04/2014	19/06/2014	SmPC and PL	Please refer to the scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation Gilenya EMEA/H/C/002202/PSUV/0027.
II/0021	Modification of the indication (section 4.1) of Gilenya to extend the patient population to patients with high disease activity despite treatment with at least one disease modifying therapy (DMT). Consequential changes were made in section 4.4 of the SmPC to include safety information relevant to switching from other immunosuppressive or immunomodulatory therapies to Gilenya. The Package Leaflet has been amended accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/04/2014	23/05/2014	SmPC and PL	Please refer to the scientific discussion Gilenya- H-002202-II-0021-AR.
IB/0028	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	28/03/2014	23/05/2014	SmPC, Labelling and PL	
II/0025	Update of section 5.2 of the Summary of Product Characteristics (SmPC) to amend the information related to the enzymes involved in the metabolic pathway of fingolimod. Section 4.5 is also updated to relocate the information related to potent inhibitors of transporter proteins under the related sub-heading. C.I.4 - Change(s) in the SPC, Labelling or PL due to	20/03/2014	23/05/2014	SmPC	After the review of the MAH updated analysis of the available data regarding fingolimod metabolism, the CHMP concluded that no further data were provided that could exclude CYP3A4 involvement in fingolimod metabolism and therefore support the changes to the SmPC proposed initially by the MAH (i.e. deletion of the reference to CYP3A4 as an enzyme involved in the metabolic pathway of fingolimod and deletion of the cautionary statement related to the interaction with CYP3A4 inhibitors). The CHMP

	new quality, preclinical, clinical or pharmacovigilance data				however recommended to reflect in the SmPC on the possible involvement of CYP isoenzymes other than CYP4F2 in fingolimod metabolism. Based on this assessment, the MAH did not pursue their initial proposed SmPC changes and agreed with the CHMP recommendations.
II/0024	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) regarding the adverse drug reactions (ADRs) based on pooled analysis of study D2301 and D2309 and latest integrated summary of safety update (ISS, 2012). Additional information is included regarding concomitant use of corticosteroid and posterior reversible encephalopathy syndrome (PRES) in section 4.4. The warning regarding varicella zoster virus (VZV) is updated to ascertain appropriate assessment of patient immunity to VZV prior to treatment. Section 4.2 was updated regarding signs of treatment related abnormalities present prior to switching therapy to Gilenya and the introductory efficacy/safety paragraph of section 5.1 was complemented by mentioning the third study completed after authorisation. Annex II and Sections 2 and 4 of the Package Leaflet were amended accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/03/2014	23/05/2014	SmPC, Annex II and PL	After review of the latest MAH safety analyses, the CHMP recommended the following main safety changes: - Neutropenia was replaced by cytopenia regarding the signs of relevant treatment related abnormalities when switching directly therapy to Gilenya. - Some ADRs were grouped (hepatic enzymes increases) and some frequencies were updated: hepatic enzyme increases, sinusitis, macular oedema, atrioventricular blocks and reduction in values for forced expiratory volume. This resulted in changes from common to very common adverse reactions (ADRs) for hepatic enzyme increases and sinusitis. - The overall rate of infections was updated. Herpes infection was added as a more common lower respiratory tract infection seen in Gilenya treated patients but observed at a lesser extent than bronchitis. The terms “influenza viral infection” and “tinea infections” were replaced by “influenza” and “tinea versicolor”, respectively, as considered as a more accurate description of these ADRs. - The following ADRs were deleted: gastroenteritis, paraesthesia, eye pain and weight decreased. - PRES was included as a warning with physicians advised to stop Gilenya treatment if PRES is suspected. - The existing warnings to ascertain appropriate assessment of patient immunity to VZV prior to treatment

					and on the concomitant use of corticosteroids were strengthened.
PSUV/0023	Periodic Safety Update	24/10/2013	18/12/2013	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation for PSUV/0023.
II/0020	Update of section 4.8 of the SmPC to add information on Haemophagocytic syndrome (HPS) following 2 case reports with Gilenya and as per the PRAC/CHMP request. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2013	25/11/2013	SmPC	Following a safety signal regarding the occurrence of 2 fatal cases of haemophagocytic syndrome with fingolimod, the PRAC/CHMP recommended an update of section 4.8 of the SmPC to reflect this information as well as to issue a Direct Healthcare Professional Communication (DHPC) with the aim of raising awareness on this risk and communicate about the difficulties of diagnosing HPS and the risk of a worse outcome when the diagnosis is delayed. Section 4.8 was updated as follows: - Very rare cases of haemophagocytic syndrome (HPS) with fatal outcome have been reported in patients treated with fingolimod in the context of an infection. HPS is a rare condition that has been described in association with infections, immunosupression and a variety of autoimmune diseases.
II/0019	Update of section 4.4 of the Summary of Product Characteristics (SmPC) to specify the periodicity of complete blood count (CBC) following assessment of the responses to the CHMP conclusions on the first PSUR (PSU 017.2). In addition, update of the Product Information in accordance with the latest QRD template (version 9) including addition of the black symbol and explanatory statements related to additional monitoring.	24/10/2013	25/11/2013	SmPC, Annex II and PL	Following their assessment of PSUR 1 for Gilenya, the CHMP requested the MAH to review all serious cases reporting leucopenia and lymphopenia with at least important information such as time to onset and outcomes. Incidence of infections in clinical trials was found greater in groups of patients with a nadir lymphocyte count <0.2x109/L than in group 0.2-0.4x109/L and >0.4x109/L. In post-marketing, the lymphocytes counts were unknown for a significant number of cases so a correlation between infections and lymphocyte count could not be excluded.

	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				Subsequently to these findings and taking also into account the data from last PSUR regarding fatal cases related to infections, the CHMP considered relevant to specify a periodicity for the complete blood count (CBC) in the SmPC. An update of the existing warning was made recommending assessment of CBC at month 3 and at least yearly thereafter.
II/0015	Update of the Summary of Product Characteristics (SmPC) regarding the existing warning on bradyarrhythmia (section 4.4) and the occurrence of lymphoma (section 4.8), following assessment of the second PSUR. In addition, section 4.8 has been updated accordingly and hypotension has been added as an associated symptom of bradyarrhythmia. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	25/04/2013	25/11/2013	SmPC	Following their assessment of PSUR 2 for Gilenya, the CHMP requested the MAH to review available data regarding the bradyarrhythmia effect of fingolimod and the occurrence of lymphoma. Subsequently to assessment of the presented analyses, the Product information has been updated to include the following concepts: - Section 4.4: after the first dose, the decline in heart rate starts within one hour, and is maximal within 6 hours. This post-dose effect persists over the following days, although usually to a milder extent, and usually abates over the next weeks. With continued administration, the average heart rate returns towards baseline within one month. However individual patients may not return to baseline heart rate by the end of the first month. - Section 4.8: there have been cases of lymphoma of different varieties, in both clinical studies and the post-marketing setting, including a fatal case of Epstein-Barr virus (EBV) positive B-cell lymphoma. The incidence of lymphoma (B-cell and T-cell) cases was higher in clinical trials than expected in the general population. In addition, section 4.8 has been updated to be in line with section 4.4 regarding the information on the bradyarrhythmia effect and to include hypotension as an associated symptom as follows: bradycardia was generally

					asymptomatic but some patients experienced mild to moderate symptoms, including hypotension, dizziness, fatigue and/or palpitations, which resolved within the first 24 hours after treatment initiation.
IG/0296/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	24/04/2013	n/a		
II/0012/G	This was an application for a group of variations. Group of variations consisting of: 1) update of section 5.1 of the SmPC to include efficacy results of D2301E1 following assessment of FUM 7; 2) update of section 5.1 of the SmPC to include efficacy results of D2302E1 following assessment of FUM 8 and 3) update of section 5.1 of the SmPC to include efficacy results of D2309 following assessment of FUM 9. Annex II was also updated in accordance with the latest template. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and	21/02/2013	25/11/2013	SmPC and Annex II	Based on the review of the submitted studies, the CHMP considered that their results are relevant to the benefit-risk profile of Gilenya and confirm its efficacy in the approved indication. The CHMP therefore accepted to include a description of the results in section 5.1 of the SmPC.

	Veterinary Medicinal Products - Other variation				
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
II/0013	Update of section 4.4 of the SmPC related to monitoring of bradyarrhyhthmia to include a recommendation for the same first dose monitoring in specific situations when treatment is re-initiated after it was interrupted (reference is also made in section 4.2) and to recommend repeated first dose monitoring for the second dose in patients requiring pharmacological intervention after the first dose. Annex II and the Package Leaflet have been amended accordingly. Changes to the Product Information were also made in accordance with the latest QRD templates and the contact details of the local representative in Malta was updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	13/12/2012	25/11/2013	SmPC, Annex II, Labelling and PL	Based on the SmPC recommendation, all patients starting treatment with Gilenya should have their heart activity monitored before receiving the first dose of the medicine and continuously for at least six hours thereafter as some patients may develop heart problems such as bradycardia (a slow heart rate) or atrioventricular block (a problem with the conduction of electricity in the heart). The SmPC of Gilenya also recommends that this first dose monitoring be repeated if a patient, who was treated for more than 1 month with Gilenya and stopped taking it for two weeks or more, re-starts treatment. The timeframe of Gilenya therapy interruption has been investigated by the MAH using pharmacokinetics, pharmacokinetic/pharmacodynamic models and titration data to better define when such monitoring should be considered. Based on these data, the CHMP recommended to extend the current advice for heart activity monitoring in case of re-initiation of treatment to the following situations: 1) treatment is interrupted for one day or more during the first 2 weeks of treatment, 2) treatment is interrupted for more than 7 days during weeks 3 and 4 of treatment. In addition, such monitoring should be repeated for the second dose in patients requiring pharmacological intervention during the first dose.
II/0010	Update of section 4.8 of the SmPC in relation to posterior reversible encephalopathy syndrome	18/10/2012	22/11/2012	SmPC and PL	On the basis of the data submitted, the CHMP considered that this present applicant fulfilled the request for updating

	(PRES) following assessment of the first European PSUR. Section 4 of the Package Leaflet (PL) has been amended accordingly. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				the Product Information to include that PRES were also observed with the 0.5 mg dose used in the approved indication. The following information has been reflected in the Product Information: - Section 4.8: In clinical studies, rare events involving the nervous system occurred in patients treated with fingolimod at higher doses (1.25 or 5.0 mg) including ischemic and haemorrhagic strokes, posterior reversible encephalopathy syndrome and neurological atypical disorders, such as acute disseminated encephalomyelitis (ADEM)-like events. Rare cases of posterior reversible encephalopathy syndrome have also been reported at doses of 0.5 mg in both the clinical and the post-marketing setting. - Section 4: Rare: A condition called posterior reversible encephalopathy syndrome (PRES). Symptoms may be headache, confusion, seizures and/or vision disturbances.
IB/0014	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	07/11/2012	25/11/2013	SmPC, Labelling and PL	
IG/0209/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	17/08/2012	n/a		

A20/0008	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 18 January 2012, the opinion of the CHMP on measures necessary to ensure the safe use of the above mentioned medicinal product further to the CHMP review on cardiovascular adverse events following administration of the first dose and its impact on the risk-benefit balance.	19/04/2012	18/06/2012	SmPC, Annex II and PL	Please refer to the assessment report: EMEA/H/C/2202/A-20/008
IG/0148/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	22/02/2012	n/a		
N/0007	The Marketing Authorisation Holder (MAH) took the opportunity to update "Liver function tests" in section 2 of the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/02/2012	18/06/2012	PL	

IA/0006/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites	15/12/2011	n/a		
II/0002	Update of sections 4.4 and 4.8 of the SmPC to revise the time of occurrence of liver enzymes elevations and related recommendation on monitoring. Annex II was consequently updated in accordance with the latest QRD templates and an editorial change was made to the address of the manufacturer for batch release regarding the city name. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/10/2011	14/12/2011	SmPC and Annex II	On the basis of the submitted data, the CHMP recommended to revise the time of occurrence of liver enzymes elevations and related recommendation on monitoring. The relevant text resulting from this variation is as follows: Section 4.4: 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 should be monitored at Months 1, 3, 6 ,9 and 12 on therapy and periodically thereafter. If liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted, including serum bilirubin and alkaline phosphatase (ALP) measurement. With repeated confirmation of liver transaminases above 5 times the ULN, treatment with Gilenya should be interrupted and only re-commenced once liver transaminase values have normalised. Sections 4.4 and 4.8: In clinical studies, transaminase elevations occurred at any time during treatment although the majority occurred

					within the first 12 months.
IG/0113/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	11/11/2011	n/a		
IG/0109	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	30/09/2011	n/a	Annex II	
IA/0001/G	This was an application for a group of variations. B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	28/04/2011	28/04/2011	SmPC and Labelling	