Pegasys

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
IB/0121	B.I.z - Quality change - Active substance - Other variation	21/08/2024	n/a		
II/0119/G	This was an application for a group of variations. Grouped application consisting of:	27/06/2024	05/08/2024	SmPC, Labelling and PL	Please refer to Scientific Discussion 'Pegasys-H-C-000395-II-0119-G'.

[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).

	Extensions of indication to include treatment of Polycythaemia Vera (PV) and Essential thrombocytopenia (ET) for PEGASYS for the pre-filled syringes, based on published data of clinical studies conducted in support of the efficacy and safety of Pegasys for the treatment of ET and PV. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.2 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.3. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0120	B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	25/07/2024	n/a		
PSUSA/9254/ 202307	Periodic Safety Update EU Single assessment - peginterferon alfa-2a	08/02/2024	n/a		PRAC Recommendation - maintenance
II/0115	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	19/10/2023	n/a		

IAIN/0118/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	11/10/2023	05/08/2024	SmPC, Annex II, Labelling and PL	
IB/0116	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	15/09/2023	n/a		
IA/0114	A.7 - Administrative change - Deletion of manufacturing sites	15/03/2023	n/a		
II/0112	Update of section 4.8 of the SmPC in order to include information on post-treatment recovery in growth based on final results from study YV25718 listed as a category 3 study in the RMP; this is a Phase IIIb parallel group, open label study of pegylated interferon alfa-2a monotherapy (PEG-IFN, RO0258310) compared to untreated control in children with HBeAg-Positive Chronic Hepatitis B in the immune active phase. The RMP version 9.1 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	29/09/2022	28/11/2022	SmPC and PL	The following information regarding recovery of post-treatment growth in children was added to section 4.8 of the SmPC, under the sub heading for Children and Chronic hepatitis B, where study YV25718 is described: "Post-treatment recovery in growth was observed in the majority of patients in short-term (81% up to 2 years) and long-term follow-up (82% up to 5 years) studies." For more information, please refer to the Summary of Product Characteristics.

IAIN/0113	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	16/05/2022	n/a		
IAIN/0111	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	17/12/2021	28/11/2022	Annex II and PL	
T/0110	Transfer of Marketing Authorisation	28/07/2021	12/08/2021	SmPC, Labelling and PL	
IA/0109	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	09/03/2021	n/a		
IB/0108	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/03/2021	16/04/2021	SmPC and PL	
IB/0107	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	03/03/2021	n/a		
PSUSA/9254/202007	Periodic Safety Update EU Single assessment - peginterferon alfa-2a	11/02/2021	n/a		PRAC Recommendation - maintenance
IAIN/0106	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/12/2020	16/04/2021	SmPC	

IB/0104	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/10/2020	16/04/2021	SmPC, Annex II, Labelling and PL	
IA/0103	B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form	07/05/2020	16/04/2021	SmPC, Labelling and PL	
II/0101	Submission of an updated RMP version 9.0 in order to remove the NV25361 study (category 3 study); in addition, the YV25718 (study to establish the efficacy and safety of PEG-IFN monotherapy in children from 3 to less than 18 years of age with CHB) long term follow up milestone is amended from Q3 2020 to Q4 2021. The classification of some risks is also amended as per revision 2 of Module V of GVP including updates in the epidemiology section. 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	06/09/2018	n/a		
N/0102	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018	16/04/2021	PL	
II/0099/G	This was an application for a group of variations.	26/04/2018	n/a		

	A.7 - Administrative change - Deletion of manufacturing sites 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 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 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 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) 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor				

	changes to an approved test procedure 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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				

	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method				

	B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
T/0100	Transfer of Marketing Authorisation	20/02/2018	15/03/2018	SmPC, Labelling and PL	
II/0098/G	This was an application for a group of variations. B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	22/02/2018	n/a		

	control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
PSUSA/9254/ 201707	Periodic Safety Update EU Single assessment - peginterferon alfa-2a	08/02/2018	n/a		PRAC Recommendation - maintenance
II/0091	Extension of indication to include the use of Pegasys in the treatment of paediatric patients from 3 to less than 18 years of age with chronic Hepatitis B in the immune-active phase; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add efficacy and safety information from study YV25718. The Package Leaflet is updated in accordance. An updated RMP (version 8.3) was agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	12/10/2017	10/11/2017	SmPC and PL	Please refer to Scientific Discussion Pegasys-H-C-395-II-91
IA/0096	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	13/07/2017	n/a		
IA/0095	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	16/06/2017	10/11/2017	SmPC, Labelling and	

				PL	
II/0092	Update of section 5.1 of the SmPC in order to add information on the predictive value of on-treatment biomarkers for final treatment response based on the final report from a systematic review and individual patient data meta-analysis of PEG-IFN studies. A cross-reference is added to section 4.2 of the SmPC accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	05/05/2017	10/11/2017	SmPC	A section on predictability of response is introduced in the SmPC. A patient-level meta-analysis of 9 Pegasys clinical studies (n=1,423) in CHB HBeAg positive and HBeAg-negative patients demonstrated that HBsAg and HBV DNA levels at Week 12 of treatment, are predictive of final treatment outcome at Week 24 post-treatment in certain genotypes. Operating characteristics of these biomarkers are presented in Table 11. No single biomarker with a cut-off can be identified to optimize all the operating characteristics (negative predictive value [NPV], sensitivity, specificity) and practical characteristics (simplicity, convenience). Consideration for early treatment discontinuation should be evaluated in the context of a particular clinical situation. For HBeAg-positive patients with HBV genotype B and C infection, HBsAg > 20,000 IU/mL or HBV DNA > 8 log10 IU/mL at Week 12 following commencement of treatment is associated with high likelihood of failure to achieve HBeAg seroconversion and HBV-DNA <2,000 IU/mL at 24 week post-treatment (NPV > 90%). For HBV genotype A and D, subgroup size was insufficient to be analyzed. For HBeAg-negative patients with HBV genotype D infection, HBsAg > 20,000 IU/mL or HBV DNA > 6.5 log10 IU/mL at Week 12 following commencement of treatment is associated with high likelihood of failure to achieve HBV-DNA <2,000 IU/mL and ALT normalization at Week 24 post treatment. HBV genotype A subgroup size was insufficient to be analyzed. No biomarker can be identified with acceptable performance for HBeAg-negative patients with HBV genotype B or C infection.

					Other published on-treatment biomarkers that are predictive of the final outcome of Pegasys treatment may be considered.
IA/0094/G	This was an application for a group of variations. A.z - Administrative change - Other variation A.z - Administrative change - Other variation A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	28/04/2017	n/a		
IA/0093/G	This was an application for a group of variations. B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits 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	05/04/2017	n/a		
II/0089	Update of sections 4.2 and 5.2 of the SmPC in order to update the information on the use of the medicinal product in patients with mild, moderate and severe renal impairment. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder took	15/09/2016	14/10/2016	SmPC and PL	

	the opportunity to bring the PI in line with the latest QRD template version 9.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
N/0090	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2016	14/10/2016	Labelling	
IA/0088	A.7 - Administrative change - Deletion of manufacturing sites	28/06/2016	n/a		
IB/0087	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	14/06/2016	01/08/2016	SmPC, Labelling and PL	
IA/0086	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	10/03/2016	n/a		
IAIN/0085	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	08/01/2016	01/08/2016	SmPC, Labelling and PL	
IB/0082	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/09/2015	01/08/2016	SmPC and PL	
IA/0084	B.II.e.3.c - Change in test procedure for the immediate packaging of the finished product -	16/07/2015	n/a		

	Deletion of a test procedure if an alternative test procedure is already authorised				
IA/0083/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 procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	16/07/2015	n/a		
IG/0573	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	01/07/2015	n/a		
IB/0080	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	21/04/2015	n/a		
PSUV/0077	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
IB/0079	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	09/12/2014	n/a		

IG/0497	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	18/11/2014	n/a		
II/0076	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/10/2014	n/a		
II/0075	Update of sections 4.4 and 4.8 of the SmPC based on data from the long term follow up study to the paediatric study NV17424. The package leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	15/10/2015	SmPC and PL	The MAH submitted the final Clinical Study Report of paediatric study NV17424 (Pegylated interferon +/- ribavirin for Children with HCV Long Term Follow-Up (PEDS-C LTFU) with this Type II Variation. Following review of the results from this study, the MAH updated the existing wording on growth and development (children and adolescents) included in sections 4.4 and 4.8 of the EU SmPC to reflect the long-term follow-up study results. Consequential changes will be made to the Annexe IIIB (Package Leaflet).
II/0073	Extension of Indication for Pegasys to include the use of other products used for the treatment of Hepatitis C. The PL is updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/03/2014	28/04/2014	SmPC and PL	Please refer to the assessment report: EMEA/H/C/000395/II/73
II/0074/G	This was an application for a group of variations. additional site responsible for the manufacturing and QC testing of the finished product	25/04/2014	n/a		

	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold 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				
PSUV/0072	Periodic Safety Update	20/02/2014	23/04/2014	SmPC and PL	Please refer to: H-395-PSUV-72 "Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation."
II/0071	Update of section 4.4 of the SmPC to include a statement on traceability of biological medicinal products. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2013	23/04/2014	SmPC	To facilitate the identification and traceability of a biological medicinal product which is the subject of a suspected adverse reaction report, a statement recommending the recording (or stating) of the trade name of the administered product in the patient file was added to the Pegasys SmPC.
II/0070	Update of section 4.4 of the SmPC to include information on use in patients with co-occurring substance use disorder. The PL is updated accordingly. In addition, the MAH took this opportunity to bring the PI in line with the latest QRD	24/10/2013	23/04/2014	SmPC, Annex II and PL	The MAH has included in the Pegasys SmPC a warning on the increased risk of development or exacerbation of psychiatric disorders in patients with co-occurring substance use disorder when treated with an alpha interferon. While a review of the MAH's safety database did

	template version 9 and to include minor editorial changes and corrections in the SmPC and PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				not reveal any reports of development or exacerbation of psychiatric disorders in patients with substance use disorder when treated with Pegasys, this warning is present in the product information of ribavirin, which is normally co-prescribed with Pegasys. Thus, for consistency this warning has also been reflected in the Pegasys product information.
N/0069	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/10/2013	23/04/2014	PL	Inclusion of additional local representative of the MAH for the new member state Croatia.
IB/0068	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	25/06/2013	n/a		
IG/0298	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/04/2013	n/a		
X/0059/G	This was an application for a group of variations. Extension of the marketing authorisation to include a new 90 mcg strength of pre-filled syringe and extension of the indication to include the treatment of chronic hepatitis C in paediatric patients aged 5 years and older with consequential changes to the SmPC and PL. The MAH further took the opportunity to update the PI in line with the latest QRD template (version 8.2) and to remove from Annex II the Nutley manufacturing site, which was withdrawn in a previous variation.	17/01/2013	13/03/2013	SmPC, Annex II, Labelling and PL	Please refer to the assessment report : EMEA/H/C/000395/X/59/G

	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				
IB/0066/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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)	12/12/2012	n/a		
II/0065/G	This was an application for a group of variations. Addition of manufacturing site for the finished product B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products. B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished	15/11/2012	n/a		

	product - Other variation				
A20/0060	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 15 December 2011, the opinion of the CHMP on measures necessary to ensure the quality and the safe use of the above mentioned medicinal product further to the inspection findings at the manufacturing site Roche Carolina Inc. (RCI), Florence, in the United States of America (USA), to assess the impact thereof on the risk-benefit balance of Pegasys and to give its opinion whether the marketing authorisation of this product should be maintained, varied, suspended or withdrawn.	19/07/2012	28/09/2012		Please refer to the assessment report : EMEA/H/C/395/A-20/0060
IB/0064	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	20/09/2012	n/a		
II/0058/G	This was an application for a group of variations. To introduce an additional manufacturing site for PEGASYS vials and pre-filled syringes B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.	15/03/2012	n/a		

	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/03/2012	28/09/2012	PL	
IB/0061	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	22/02/2012	n/a		
IA/0062	A.7 - Administrative change - Deletion of manufacturing sites	10/02/2012	n/a		
II/0055	Update of section 4.8 of the SmPC at the request of the CHMP further to the assessment of PSUR 12 in order to incorporate post-marketing adverse events into the tabulated list of adverse reactions. The PL has been updated 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 -	20/10/2011	14/12/2011	SmPC and PL	During assessment of PSUR 12 of Pegasys the CHMP identified that a number of adverse reactions were listed with the "frequency unknown" under the heading "Post marketing adverse events" in section 4.8 of the Pegasys SmPC. As such an update of this section of the SmPC has taken place in order to incorporate post-marketing adverse reactions into the tabulated list of adverse reactions and where possible to indicate the frequency of the adverse reaction.

	Change(s) with new additional data submitted by the MAH				
IB/0057	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	03/10/2011	n/a		
II/0052/G	This was an application for a group of variations. Changes in the manufacturing process of the active substance. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	22/09/2011	22/09/2011		

	or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate 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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0056	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol	09/09/2011	n/a	SmPC and Labelling	

IA/0053	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	10/08/2011	n/a	SmPC, Labelling and PL	
II/0050	Update of Summary of Product Characteristics and Package Leaflet Further to request of the CHMP on 16 December 2010, as part of a class-labelling change, the Product Information of ribavirin and the interferon-containing products is updated to remove from SmPC section 4.6 "Pregnancy and Lactation" the requirement of double contraceptive measures for a treated woman and male patients. The package leaflet is updated 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	19/05/2011	29/06/2011	SmPC and PL	A review of reported relevant prospective cases of maternal and paternal exposure to ribavirin has been carried out. Only a limited number of cases are available. However, a large number of data would be necessary to draw a definitive conclusion on the teratogenic potential of ribavirin. The malformative risk is possible in human, but it is not confirmed. For paternal exposure, the malformative risk is unlikely in humans. Taking into account the number of reference cases outnumbering 300 after paternal exposure with no increase of congenital anomaly risk, it is recommended to remove the requirement of double contraceptive measures for a treated woman and male patient. For female patients, the CHMP agreed that they should be instructed to use an effective contraceptive. For male patients, the CHMP recommended that either male patients or their female partners of childbearing age must be advised to use an effective contraceptive.
II/0047/G	This was an application for a group of variations. To add a new staked-in needle pre-filled syringe in a disposable autoinjector. B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological	19/05/2011	29/06/2011	SmPC, Labelling and PL	

	medicinal products B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products 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 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 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 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				
IB/0049/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	13/05/2011	n/a		

II/0048	Update of section 4.3 and 4.5 to include a contraindication for the use of Pegasys in combination with telbivudine. The package leaflet is updated accordingly further to request by the CHMP. 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	17/03/2011	18/04/2011	SmPC and PL	A clinical trial investigating the efficacy and the safety of telbivudine in combination with pegylated interferon alfa-2a (Pegasys) for the treatment of Hepatitis B demonstrated that the combination of these two medicinal products increases the risk of peripheral neuropathy. Subsequently the product information of Pegasys has been updated to contraindicate the combined use of telbivudine and Pegasys.
IB/0046/G	This was an application for a group of variations. B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition 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)	06/12/2010	n/a		
II/0045	Update of Section 4.2, 4.3 and 4.4 of the SmPC with information related to the posology of HIV/HCV co-infected patients and safety related information from study NV18209. Update of Summary of Product Characteristics	20/05/2010	02/07/2010	SmPC	Study NV18209 was carried out in co-infected patients with HIV/Hepatitis C Genotype 1 in order to confirm the safety of the 1000/1200 mg dose of ribavirin. Taking into account the outcome of the study and other available evidence the CHMP agreed that the posology in these mono-infected individuals should also be applicable for HCV/HIV co-infected patients with Genotype 1. Furthermore it was noted that in most cases increases in bilirubin and decreases in albumin are not likely to be reflective of a deterioration of hepatic function and are rather a side effect

					of treatment. As such prescribers are alerted to this possibility.
II/0044	Update of Section 4.4 and 4.8 of the SPC to include information on liver and renal transplant rejection. This follows a request of the CHMP made in the context of the assessment of PSUR 9 (period covered: 05.07.07 - 04.07.08). Section 4.8 has been reorganizing for greater clarity. Section 4.2 is updated to provide a clarification. A minor correction has been made to the package leaflet. Update of Summary of Product Characteristics and Package Leaflet	20/05/2010	02/07/2010	SmPC and PL	Data from a literature review and a cumulative review of transplantation rejection reported in association with the use of Pegasys and IFN therapy in general found has been reviewed. Nineteen cases with acute and/or chronic liver rejection and five reports of kidney transplant rejection were identified. The conclusions from the literature publications were conflicting. Overall the data provided includes enough evidence to conclude that occurrence of liver and renal graft rejections may be associated with treatment with interferon alpha, including treatment with Pegasys. This has been reflected in the SmPC.
II/0043	Update of Summary of Products Characteristics and Package Leaflet. Update of sections 4.4, 4.5 and 4.8 of the SPC to include a drug-drug interaction between ribavirin and azathioprine and safety information on homicidal ideation. The PL was updated accordingly. The MAH took the opportunity to amend the SPC and product labelling due to a change in the design of the packaging in compliance with QRD. In addition minor corrections have been made to the Greek PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/09/2009	23/10/2009	SmPC, Labelling and PL	Following a literature publication and a review of the MAH's database on the interaction between ribavirin and azathioprine metabolism inducing myelosuppression, the SPC has been amended with information on the drug-drug interaction that may increase the risk of azathioprine-related myelotoxicity. The use of peginterferon alfa-2a and ribavirin concomitantly with azathioprine should be avoided. In addition, a Pharmacovigilance cumulative assessment of cases involving Pegasys alone or in combination with ribavirin reporting adverse events of homicide or homicidal ideation was undertaken for all cases entered onto the MAH's Drug Safety database. Some psychiatric symptoms were already included in the current SPC. Homicidal ideation has been added to the list of psychiatric undesirable effects.

II/0042	Update of Summary of Product Characteristics Update of the section 5.1 and section 4.2 of the SPC with data from ACCELERATE clinical study to justify the 800 mg flat dose of ribavirin in patients infected with HCV genotype 2 or 3 further to a request from CHMP made in the context of FUM 041.1. Update of Summary of Product Characteristics	23/07/2009	21/08/2009	SmPC	The overall evidence for the use of an 800 mg flat dose of ribavirin in patients with genotype 2/3 treated for 24 weeks is considered sufficiently solid, as comparative studies have not clearly demonstrated any efficacy advantage of a higher dose, to outweigh a higher risk of exposure related adverse effects. No comparative data are presently available concerning the relative efficacy of an 800 mg flat dose and a higher, weight based regimen in patients treated for a shortened duration, the CHMP therefore considered that it is unclear what dose of ribavirin should be used if treatment is started in a patient where a shortened duration of therapy is planned in case of a Rapid Viral Response. This is reflected in the SPC.
II/0041	Update of Summary of Product Characteristics and Package Leaflet Further to the review of PSUR 9 of Pegasys section 4.4 of the SPC is updated to include bipolar disorders, mania, sepsis, and Vogt-Koyanagi-Harada disease. The interaction between Telbivudine and Pegasys is reflected in section 4.5 of the SPC and the following adverse reactions are included in section 4.8 of the SPC: sepsis, ischaemic colitis, Vogt-Koyanagi-Harada disease, Pure Red Cell aplasia (PRCA), peripheral ischaemia and bipolar disorder / mania. The package leaflet is updated accordingly. The details of the local representative in Latvia are also updated. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	21/08/2009	SmPC and PL	Further to the assessment of PSUR 9 (period covered 05.07.07 - 04.07.08) amendments are made to the SPC. In Section 4.4 Sepsis is mentioned in the context of other infections. A warning concerning the relation of serous retinal detachment to pre-disposing autoimmune uveitis/suspected Vogt-Koyanagi-Harada disease is also included and bipolar disorder and mania are mentioned. In Section 4.5 a warning concerning the interaction between Telbivudine and Pegasys and the possible increased risk for peripheral neuropathy is included. In Section 4.8 the following adverse reactions are included: sepsis, ischaemic colitis, peripheral ischaemia, bipolar disorder / mania, Vogt-Koyanagi-Harada disease and Pure Red Cell aplasia (PRCA).

II/0040	Change(s) to the manufacturing process for the finished product. Change(s) to the manufacturing process for the finished product	29/05/2009	11/06/2009		
II/0039	Change(s) to the manufacturing process for the active substance Change(s) to the manufacturing process for the active substance	29/05/2009	11/06/2009		
II/0038	Update of Summary of Product Characteristics	19/03/2009	08/04/2009	SmPC	
II/0036	Extension of indication to include the treatment of patients who have failed previous treatment with interferon alfa (pegylated or non-pegylated) in combination therapy with ribavirin. Extension of Indication	23/10/2008	28/11/2008	SmPC and PL	Please refer to the scientific discussion Pegasys-H-395-II-36 for further information
II/0037	Update of section 4.4 of the SPC further to a request of the CHMP following the evaluation of follow up measure FUM 12. Data from the HALT-C study (NR15963) of HCV non-responder patients with varied degrees of fibrosis is reflected. Update of Summary of Product Characteristics	25/09/2008	30/10/2008	SmPC	HALT-C was a randomised controlled trial of peginterferon alfa-2a (90 µg per week) for 3.5 years versus no treatment in patients with chronic hepatitis C and advanced fibrosis who were non responders to prior therapy with peginterferon and ribavirin. 1050 patients were randomised (517 treatment, 533 control). The study was negative with respect to the primary endpoint of clinical events and suggested that long-term therapy with peginterferon did not reduce the rate of disease progression in patients with

					chronic hepatitis C and advanced fibrosis or cirrhosis.
II/0035	Update of section 4.8 of the SPC to include the following adverse reactions; fungal, bacterial and viral infections; cerebral ischaemia; serious retinal detachment; cardiomyopathy; vasculitis; rhabdomyolysis and renal insufficiency further to a request of the CHMP made in the context of the assessment for PSUR 9. The package leaflet is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	20/06/2008	SmPC and PL	Further to the evaluation of PSUR 9 (covering the period 9 October 2007 to 4 July 2007) the CHMP requested the MAH to include a number of adverse drug reactions in the SPC. For cerebral ischaemia, retinal detachment, cardiomyopathy, vasculitis, rhabdomyolysis and renal insufficiency, a cumulative search of the MAH database was performed. For bacterial, fungal and viral infections, the MAH compiled safety data from pivotal HCV and HBV trials to address the CHMP request. Based on this review, 313 viral events, 72 fungal events, and 242 bacterial events were identified. Regarding cerebral ischemia, 92 cases were identified. There were 29 Pegasys related cases of retinal detachment and Vogt-Koyanagi-Harada disease. A review carried out by the MAH identified that only the serous type of retinal detachment may be associated with the use of alpha interferons in HCV patients. As such serous retinal detachment has been included in the SPC. Regarding cardiomyopathy and vasculitis, 30 cases and 36 cases were identified respectively.
II/0033	Update of sections 4.2 and 5.1 of the SPC to shorten the treatment duration in patients with Genotype 2 and 3 with a rapid viral response from 24 weeks to 16 weeks based on a retrospective analysis of study NV17317. The package leaflet is updated accordingly. The MAH takes the opportunity to make corrections to the Romanian and Czech product information.	24/04/2008	20/06/2008	SmPC and PL	A retrospective subgroup analysis of study NV17317 examined the Sustained Virologic Response of patients who where HCV RNA negative by week 4 and had a Low Viral Load at baseline. The results suggest that 16 weeks of treatment may be an alternative option for this subgroup. However 16 weeks of treatment may be associated with a lower chance of treatment response and is associated with a higher risk of relapse than treatment for 24 weeks. The overall long-term clinical impact associated with a

	Update of Summary of Product Characteristics and Package Leaflet				shortening of the treatment duration from 24 to 16 weeks remains unknown. This has been reflected in the SPC.
II/0034	Change(s) to the manufacturing process for the active substance	21/02/2008	25/02/2008		
II/0032	Update of section 4.8 of the SPC to include the adverse event "dehydration" further to a review carried out by the MAH. Furthermore the frequency categories for adverse reactions included in section 4.8 are updated following a request from the CHMP. The MAH also takes the opportunity to make a correction to the frequency category of the adverse event "weight decreased" in section 4.8 of the SPC. The package leaflet is updated accordingly. The details of the Estonian local representative are updated in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	18/10/2007	19/11/2007	SmPC and PL	Cumulatively 145 cases of "dehydration" were reported up until January 2007. About 50% of the reports referred to events occurring within the first two months of therapy. An association with diarrhoea and vomiting was seen. Similarly flu like symptoms may contribute. Twenty cases of dehydration were reported in a total of 5,967 patients in clinical trials. The estimated rate was thus about 0.3%, therefore in the category "uncommon".
II/0031	Update of sections 4.2, 4.4 and 4.5 of the SPC further to the assessment of a follow-up measure concerning HIV-HCV co-infection to reflect new information about the status of knowledge regarding dosing of HIV-HCV co-infected population and to reflect new precautions regarding the increased risk of anaemia when dosing alfa-interferons with ribavirin and zidovudine. The PL has been updated accordingly. Update of Summary of Product Characteristics and	18/10/2007	19/11/2007	SmPC and PL	Patients co-infected with HIV and HCV may include zidovudine as part of their antiretroviral regimen. Available data suggest an increased risk for anaemia in patients treated with interferon, ribavirin and zidovudine. Therefore prescribers are warned that this combination is not recommended. Consideration should be given to replacing zidovudine in a combination antiretroviral regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia. Sections 4.4 and 4.5 of the SPC are updated accordingly. Section 4.2 has also been updated further to

	Package Leaflet				the submission of the study 'PRESCO', to reflect the status of knowledge regarding dosing and duration of treatment of HIV/HCV co-infected population.
R/0029	Renewal of the marketing authorisation.	26/04/2007	21/06/2007	SmPC, Annex II, Labelling and PL	
II/0030	Update of Summary of Product Characteristics To update section 4.5 "Interaction with other medicinal products and other forms of interaction" of the Summary of Product Characteristics (SPC) to provide additional information on concomitant treatment with methadone. The MAH took the opportunity to correct an editorial mistake in the section 4-Possible side effects of the Package Leaflet (PL). Update of Summary of Product Characteristics and Package Leaflet	24/05/2007	21/06/2007	SmPC and PL	The section 4.5 was updated following the results of a pharmacokinetic study of 24 chronic hepatitis C patient receiving methadone maintenance therapy. The study showed mean methadone levels 10 to 15% higher than at baseline. The clinical significance of this finding is unknown but patients should be monitored for signs and symptoms of methadone toxicity, specially risk of QTc prolongation in patients on a high dose of methadone.
II/0027	Update of section 4.2 and 5.1 of the SPC to shorten the treatment duration from 48 weeks to 24 weeks in patients with genotype 1 with low viral load and patients with genotype 4 who have a rapid virological response based on the results of a retrospective analysis of two pivotal trials. Update of Summary of Product Characteristics	24/01/2007	01/03/2007	SmPC	Based on a retrospective reanalysis of two peginterferon-alfa 2a pivotal studies and other available data treatment for 24 weeks may be considered in patients infected with genotype 1 with low viral load (LVL) (£ 800,000 IU/mL) at baseline or genotype 4 who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24. Prescribers are however warned that an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration. This information is reflected in section 4.2 and 5.1 of the SPC.

II/0024	Following PSUR 7 (covering the period 1 February 2005 - 31 January 2006) section 4.8 of the SPC is updated to add the adverse reactions facial palsy, convulsions, diabetic ketoacidosis and erythema multiforme. Section 4.4 is also updated with the risk of serious infections and of uncontrolled hyper- and hypoglycaemia. A warning is also included regarding periodontal disorders. The package leaflet is updated accordingly. The MAH also takes the opportunity to update the list of local representatives for Poland and Iceland in the package leaflet. In addition the MAH completed the list of local representatives in the PL to include the two new EU Member States (Bulgaria and Romania) and changed the format according to the latest EMEA/QRD template. Update of Summary of Product Characteristics and Package Leaflet	16/11/2006	04/01/2007	SmPC and PL	Section 4.4 of the SPC has been updated with the risk of serious infections and of uncontrolled hyper- and hypoglycaemia in order to adequately reflect the Company Core Data Sheet. Section 4.4 is also updated with a warning regarding the risk of periodontal disorders. Section 4.8 is updated with the following adverse effects: facial palsy, convulsion, diabetic ketoacidosis and erythema multiforme.
II/0026	Change(s) to the manufacturing process for the active substance Update of Summary of Product Characteristics Update of Summary of Product Characteristics and Package Leaflet	16/11/2006	22/11/2006		
II/0025	Update of section 4.4 "Special warnings and Precautions for use" and 5.2 "Pharmacokinetic	18/10/2006	22/11/2006	SmPC	A substudy evaluating peginterferon alfa-2a kinetics and dynamics at the end of long-term treatment in patients

	properties" of the SPC to include the time for recovery of neutrophil count and to add a new estimate of terminal half life, as requested by the CHMP further to the assessment of a pharmacokinetic and neutrophil recovery substudy on Pegasys. Update of Summary of Product Characteristics Update of Summary of Product Characteristics and Package Leaflet				with Hepatitis C showed that the absolute neutrophil count (ANC) reached normal values by 8 weeks in the majority of patients and returned to baseline in all patients in about 16 weeks. Furthermore, the terminal half-life after subcutaneous administration was showed to have a mean value of 160 hours. Based on these findings section 4.4 and 5.2 of the SPC were updated following a request by the CHMP.
IA/0028	IA_05_Change in the name and/or address of a manufacturer of the finished product	28/09/2006	n/a	Annex II and PL	
II/0023	Change(s) to the manufacturing process for the finished product	21/09/2006	25/09/2006		
II/0022	Update of section 4.4 of the SPC following a class labelling adopted by the CHMP on 23 March 2006 regarding psychiatric disorders. The Package Leaflet has been up dated accordingly. The MAH also takes the opportunity to carry out a minor correction in section 6.4 of the SPC and annexes pertaining to storage conditions to be in line with the QRD template and the MAH also carries out some minor editorial corrections. Update of Summary of Product Characteristics, Labelling and Package Leaflet	28/06/2006	20/07/2006	SmPC, Labelling and PL	Following a safety review on suicide and attempted suicide section 4.4 of the SPCs of a number of the alfa-interferon products and ribavirin were updated to include a warning on the duration of psychiatric disorders. This update occurred in September 2005. On assessment of further pharmacovigilance follow up measures the CHMP requested a class labelling to put more emphasis on psychiatric disorders in the SPC and Package Leaflet of the alfa-Interferon and ribavarin containing products. In addition the warning that psychiatric disorders may also occur after termination of treatment was included in the Pegasys SPC to align with the Interferon-alfa-2b products and ribavarin. Due to differences in the indications of these products it was not possible to propose a class labelling "text" for all

					these products. Rather the existing paragraphs pertaining to psychiatric disorders in the SPCs and Package Leaflets have been moved to the beginning of the corresponding sections and placed in a warning box in order to draw attention to these serious adverse effects.
II/0021	Update of section 4.3 of the SPC to withdraw the contraindication of Pegasys during pregnancy and lactation. Section 4.6 of the SPC will also be amended regarding the recommendations on pregnancy and lactation. This change follows the adoption of a class labelling by the CHMP on 26th January 2006 for the Interferons and Ribavirin for pregnancy and lactation. Corresponding revisions to the Package Leaflet are made. Update of Summary of Product Characteristics and Package Leaflet	27/04/2006	29/05/2006	SmPC and PL	The CHMP noted differences in the SPC's of Ribavarin and alfa-Interferon containing products regarding the contraindication to pregnancy and lactation, the recommendations on the duration of contraception and the recommendations on lactation. The CHMP agreed that in view of the available teratogenicity data for the alfa-Interferons products it should be made clear that the strict contraindication of Pegasys during pregnancy and lactation is not justified. Therefore the CHMP agreed to the withdrawal of the contraindication to pregnancy and lactation for Pegasys. However it is noteworthy that pregnancy and lactation are not recommended with use of alfa-Interferons. Further, regarding lactation, the CHMP agreed that given the importance of the treatment to the mother, prescribers should not be given a choice between initiating treatment or breastfeeding. Rather a warning should be included in Section 4.6 "Pregnancy and Lactation" that breast-feeding should be discontinued prior to treatment. The CHMP further agreed that given the teratogenic potential demonstrated for ribavirin in animal species the duration of recommended contraception following the termination of treatment should be based on the calculation of the elimination of Ribavarin that uses a maximal value of half life. Further, the CHMP maintained that separate

					recommendations should exist for female patients and male patients and their female partners. This is because the advantage of having consistent recommendations for all patients is outweighed by the fact that female patients would be advised to use contraception for 2 months more than necessary. Therefore the CHMP concluded that when Pegasys and other alfa-Interferons are used in combination with Ribavarin contraceptive measures should be used during treatment and for 4 months after treatment discontinuation in female patients and during treatment and for 7 months after treatment discontinuation in male patients and their female partners.
II/0020	Change(s) to the manufacturing process for the active substance	27/04/2006	03/05/2006		
II/0018	Update of Summary of Product Characteristics, Labelling and Package Leaflet	14/12/2005	26/01/2006	SmPC, Annex II, Labelling and PL	
IA/0019	IA_01_Change in the name and/or address of the marketing authorisation holder	25/10/2005	n/a	SmPC, Labelling and PL	
II/0015	Change(s) to the test method(s) and/or specifications for the active substance	23/06/2005	30/06/2005		
II/0014	Change(s) to the manufacturing process for the active substance	21/04/2005	27/04/2005		
II/0011	Extension of Indication	20/01/2005	23/03/2005	SmPC and PL	
IB/0016	IB_38_b_Change in test procedure of finished	02/03/2005	n/a		

	product - minor change, biol. active subst./excipient				
IA/0017	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	24/02/2005	n/a	PL	
IA/0013	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	11/02/2005	n/a		
II/0009	Extension of Indication	15/12/2004	26/01/2005	SmPC and PL	
IB/0012	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	11/01/2005	n/a	SmPC	
II/0007	Extension of Indication	16/09/2004	29/10/2004	SmPC, Labelling and PL	The Marketing Authorisation Holder applied for an extension of the therapeutic indication of all the formulations of Pegasys (peginterferon alfa-2a) to include treatment in combination with ribavirin of adult patients with chronic hepatitis C (CHC) and persistently normal alanine aminotransferase (ALT) levels with consequential changes to Sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SPC. In addition the SPC, labelling and PL were updated in accordnace to the SPC guideline and the latest QRD template. It has been estimated that 30% of patients with CHC have persistently normal ALT (defined by detectable hepatitis C virus (HCV) RNA, HCV antibodies and at least three ALT values within the normal reference range over a 6 month period). There appears to be no major difference in terms of viral load or genotype (incl. quasispecies) as compared to patients with CHC and increased ALT. Predictive factors for persistently normal ALT in case of CHC include female

					sex, age >40 years, no alcohol use and low body mass index. The long-term prognosis is ill defined. Multiple factors, relating to both the virus and the individual, may influence the benefit/risk ratio of initiating treatment in patients with chronic hepatitis C. These factors should be considered in the evaluation of each individual patient's suitability for treatment and normal ALT status per se should no longer be considered a barrier to treatment if other factors support this intervention. No additional information on clinical pharmacology was obtained during the clinical development programme presented in this application. The pivotal study designed to evaluate the clinical efficacy and safety of a pegylated IFN alfa plus ribavirin for the treatment of CHC in patients with persistently normal ALT activity was a multicentre (70), randomised, open label study (study NR16071) comparing 3 groups: · PEG-IFN 180 micrograms once weekly + ribavirin 800 mg daily for 24 weeks · PEG-IFN 180 micrograms once w
IB/0010	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	21/07/2004	21/07/2004	SmPC, Labelling and PL	
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/05/2004	n/a	PL	

II/0006	Update of or change(s) to the pharmaceutical documentation	22/10/2003	14/01/2004	Annex II	
II/0001	Update of Summary of Product Characteristics and Package Leaflet.Changes to section 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 5.2 of the SPC. The package leaflet was amended to reflect the SPC and changes also made to the list of local representatives. Update of Summary of Product Characteristics and Package Leaflet	25/04/2003	23/07/2003	SmPC and PL	Changes were made to section 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 5.2 of the SPC. The MAH applied to remove the term "histologically proven" from the section 4.1 of the SPC referring to the French Consensus Conference on Hepatitis C where it is stated that biopsy may not be necessary if a decision to treat has been made on other grounds and the primary objective is viral eradication. This is also largely in line with other National Guidelines. The viral eradication rate is sufficiently high for patients with genotype 2/3 that treatment is indicated in many cases even if the histology turns out to be benign. Therefore histology is not always needed. The CPMP agreed that the term "histologically proven" should be removed from section 4.1 but requested that a warning be added to section 4.4: "All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (ie patients with genotype 2 or 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment." The main focus of the variation was the results of study NV15942, a randomised, double blind trial comparing 24 and 48 weeks of therapy and two dosages of ribavirin in combination with Pegasys (Peg-IFN) in patients with chronic hepatitis C. As a result of the study, the MAH

					proposed changes to section 4.2, 4.4, 4.8, 5.1 and 5.2 of the SPC. Virological Sustained Response as a Function of Genotype and Viral Load (ITT) RIBAVIRIN RIBAVIRIN RIBAVIRIN RIBAVIRIN 800 1000/1200 800 1000/1200 24W (A) 24 W (B) 48 W (C) 48 W (D) Genotype 1
II/0005	Change(s) to the test method(s) and/or specifications for the active substance	24/04/2003	02/05/2003		
I/0003	01_Withdrawal of the manufacturing authorisation for a site of manufacture	26/11/2002	14/01/2003	Annex II and PL	
I/0002	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	26/11/2002	14/01/2003	Annex II and PL	
I/0004	31_Change in container shape	19/12/2002	20/12/2002		