EMA/117329/2021

Somavert

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/0098/G	This was an application for a group of variations. Variation to update the Risk Management Plan following assessment of the final results of ACROSTUDY, a multicenter, Post Authorisation	14/01/2021		SmPC and PL	Following a multicenter, Post Authorisation Safety Study (PASS) of Somavert therapy in patients with acromegaly, the relationship between pegvisomant and risk of tumour growth was analysed and it was established that the mention regarding growth hormone secreting tumours and

[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).

	Safety Study (PASS) of Somavert therapy in patients with acromegaly (procedure number EMEA/H/C/000409/II/0089), grouped with variation to update of section 4.4 of the SmPC regarding growth hormone secreting tumours, consequential to the removal of pituitary tumour growth as a potential risk from the RMP. The RMP version 2.0 has been submitted and the MAH took the opportunity to update it as per the revised version of the GVP Module V Risk Management Systems, revision 2. The Package Leaflet is updated accordingly. The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data 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				the statements regarding monitoring of the tumour growth, expansion and reduction of the GH-secreting pituitary tumours from Section 4.4 Special warnings and precautions for use should not be removed, but reworded so as to align to the wording on growth hormone secreting tumours of the SmPC for other approved acromegaly therapies.
IB/0100/G	This was an application for a group of variations. B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	22/12/2020	n/a		

	A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
II/0097	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/11/2020		SmPC and PL	
IB/0099	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/10/2020		SmPC and PL	
IB/0096	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	10/07/2020	n/a		
PSUSA/2328/ 201911	Periodic Safety Update EU Single assessment - pegvisomant	09/07/2020	n/a		PRAC Recommendation - maintenance
II/0095	B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	02/07/2020		SmPC, Labelling and PL	
IB/0094	B.II.z - Quality change - Finished product - Other variation	12/05/2020	n/a		
II/0091	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	06/02/2020	n/a		

N/0092	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/11/2019		PL	
II/0089	Submission of the final report from ACROSTUDY (Study A6291010), an open-label, global, non-interventional post-authorisation safety study (PASS) performed to monitor the long-term safety and outcomes of pegvisomant treatment in clinical practice. This final CSR relates to the Post Approval Measure MEA 059, listed as a category 3 study in the RMP. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/07/2019	n/a		n/a
IB/0090	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/03/2019	16/09/2019	SmPC	
IB/0088	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	29/01/2019	n/a		
II/0086/G	This was an application for a group of variations. 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.b - Change in the manufacturing process of	08/11/2018	n/a		

	the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation 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				
II/0084	Update of sections 4.2 and 4.4 of the SmPC to recommend an assessment of baseline levels of liver tests (LTs) [serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total bilirubin (TBIL), and alkaline phosphatase (ALP)] prior to initiation of treatment with Somavert as well as monitoring of LTs during treatment, following analysis of the interim result of study "A6291010 (ACROSTUDY) - A multicenter, post marketing surveillance study of pegvisomant therapy in patients with acromegaly – extension" as requested in procedure EMEA/H/C/000409/MEA 061.1. The PL has been updated accordingly. C.I.3.z - 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 - Other variation	13/09/2018	16/09/2019	SmPC and PL	Prior to the start of SOMAVERT, patients should have an assessment of baseline levels of liver tests (LTs) [serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total bilirubin (TBIL), and alkaline phosphatase (ALP)]. Evidence of obstructive biliary tract disease should be ruled out in patients with elevations of ALT and AST or in patients with a prior history of treatment with any somatostatin analogue. Administration of pegvisomant should be discontinued if signs of liver disease persist. For recommendations regarding initiation of SOMAVERT based on baseline LTs and recommendations for monitoring of LTs while on SOMAVERT, please refer to the Summary of Product Characteristics.
T/0087	Transfer of Marketing Authorisation	30/07/2018	23/08/2018	SmPC, Labelling and	

				PL	
IB/0083	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	09/07/2018	23/08/2018	SmPC, Labelling and PL	
IB/0085	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)	05/06/2018	n/a		
PSUSA/2328/ 201611	Periodic Safety Update EU Single assessment - pegvisomant	06/07/2017	n/a		PRAC Recommendation - maintenance
N/0082	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/06/2017	23/08/2018	Labelling	
IB/0080	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	16/03/2017	n/a		
N/0079	Update of the package leaflet in line with results of the user testing for the Somavert powder vial and solvent vial presentations. In addition the MAH took the opportunity to amendment the Instructions for Use at the end of the package leaflet to align text with the approved text for the solvent prefilled syringe label. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/10/2016	02/06/2017	PL	

II/0077	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	30/06/2016	02/06/2017	SmPC, Labelling and PL	
II/0078	Update of section 4.8 of the SmPC in order to revise frequency, order of seriousness and alignment with current MedDRA terms of the listed Adverse Drug Reactions, following re-analysis of all-causality adverse events (AEs) in the clinical trial dataset and laboratory evaluations and considering post marketing reports. The package leaflet has been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct some typographical errors and formatting in the Product information and to bring the PI in line with the 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	16/06/2016	02/06/2017	SmPC, Annex II, Labelling and PL	
IB/0076/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.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	05/08/2015	n/a		

X/0072	Annex I_2.(c) Change or addition of a new strength/potency	21/05/2015	17/07/2015	SmPC, Annex II, Labelling and PL	
N/0075	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	02/06/2017	PL	
IA/0074/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 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	30/10/2014	11/02/2015	Annex II	
IB/0073/G	This was an application for a group of variations. 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	03/09/2014	n/a		

	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				
PSUV/0070	Periodic Safety Update	12/06/2014	n/a		PRAC Recommendation - maintenance
IA/0071/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 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	31/03/2014	n/a		
II/0069	B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a	20/02/2014	n/a		

	significant impact on the quality, safety and efficacy of the medicinal product				
II/0068/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	20/02/2014	11/02/2015	Annex II	
IB/0067/G	This was an application for a group of variations. B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.c.3.b - Change in test procedure for the immediate packaging of the AS - Other changes to a test procedure (including replacement or addition)	12/12/2013	n/a		
IB/0066/G	This was an application for a group of variations. 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.1.z - Change in the specification parameters	24/10/2013	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - 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) B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation				
N/0065	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/09/2013	11/02/2015	Labelling and PL	
IB/0064	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	12/06/2013	n/a		
IB/0063	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	23/05/2013	n/a		
II/0061	To change the manufacturing process of the active substance B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	21/03/2013	n/a		

IB/0060/G	This was an application for a group of variations. 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 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	04/01/2013	n/a		
IG/0236/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	03/12/2012	n/a		
II/0057/G	This was an application for a group of variations. 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.e.4.b - Change in shape or dimensions of the container or closure (immediate packaging) - The change in shape or dimensions concerns a fundamental part, which may have a significant	18/10/2012	n/a		

	impact on the delivery, use, safety or stability of the FP				
IA/0058/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.7 - Administrative change - Deletion of manufacturing sites	14/06/2012	10/09/2012	Annex II	
IB/0056/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) 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	23/02/2012	n/a		
IB/0055/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS 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	23/02/2012	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place				
II/0051	This type II variation concerns an update of section 4.8 of the SmPC, upon request by the CHMP following the assessment of PSUR 10, in order to update the safety information regarding the ADR 'systemic hypersensitivity reactions'. In addition, the MAH took the opportunity to amend the listed terms in sections 4.8 and 4.9 to MedDRA terms, to reorder the events into MedDRA system organ class sequence, to change the frequencies of two listed ADRs and to implement changes to sections 4.8 and 4.9 in line with the SmPC guideline (Sept 2009). The Package Leaflet has been updated in accordance. Finally, the contact details of the local representative in Spain have been updated in the Package Leaflet and a statement has been added that the vial adapter (Mixject) is not marketed in all EU member states. 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	17/11/2011	19/12/2011	SmPC and PL	Systemic hypersensitivity reactions including anaphylactic/anaphylactoid reactions, laryngospasm, angioedema, generalized skin reactions (rash, erythema, pruritus, urticaria) have been reported in post marketing use. Some patients required hospitalization. Upon re-administration, symptoms did not re-occur in all patients. In support of this variation application, the MAH provided a cumulative review of all "possible hypersensitivity-related events" reported in its database. Through 31 May 2010, a total of 79 cases were identified (8.3% of the total number of pegvisomant reported cases) that encoded to at least one PT included in the search criteria. Out of these 79 cases, 42 cases reported events that did not appear to be related to a systemic hypersensitivity reaction to pegvisomant therapy. Among the 37 remaining cases (1 duplicate), 13 were assessed as serious without any fatal outcome. The nature of the reported serious AEs, mostly with short latency, the mostly favourable outcome after pegvisomant discontinuation and the absence of other more compatible aetiologies - even if six of the 36 cases reported a potentially relevant medical history associated with a high risk of a systemic hypersensitivity-related event - are all in favour of the responsibility of pegvisomant therapy in these hypersensitivity-related events. Some physio-pathological explanations have been proposed by the MAH, but no formal conclusion can be drawn regarding the aetiological mechanism. Taking into account the time course of the reporting rate of

					systemic hypersensitivity-related events compared to the time of discontinuation of latex-containing stoppers, this does not seem to imply that these are latex related allergic reactions. The MAH had previously raised the hypothesis that improper storage of the vials or of the reconstituted solution may lead to chemical degradation and/or soluble aggregates formation and thus to potential occurrence of systemic hypersensitivity reactions. However, as stated by the MAH, the Somavert formulation has been shown to protect the active molecule against stresses, e.g. shaking/agitation, exposure to high temperatures, exposure to freezing temperatures, and undue exposure to light, both in the lyophilized state and also in the liquid state. The available stability data over multiple lots manufactured over many years supports the conclusion that the product quality, as measured by chemical degradation as well as aggregate levels, is maintained over the shelf-life of the product. The risk to the lyophilized product quality through the formation of chemical and physical (i.e. aggregation) degradation products is minimal. Furthermore, appropriate instructions for storage and reconstitution that cover the risk of mishandling are already provided in the SmPC and in the Package Leaflet. No data on antibodies (to GH or to pegvisomant) titers in patients having experienced systemic hypersensitivity events are currently available.
IA/0053/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	05/10/2011	n/a		

	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				
II/0047/G	This was an application for a group of variations. Additional facility for the active substance manufacture and changes to the active substance manufacturing process. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	17/03/2011	18/04/2011	Annex II	
IA/0050	A.7 - Administrative change - Deletion of manufacturing sites	17/03/2011	n/a		
IA/0049	A.7 - Administrative change - Deletion of manufacturing sites	11/11/2010	n/a		
IA/0048	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)	11/11/2010	n/a		

IB/0045	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	08/09/2010	n/a		
IA/0046	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	26/08/2010	n/a		
IA/0044	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)	16/07/2010	n/a		
IA/0043	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	16/07/2010	n/a		
IB/0042	Change in the control of the drug product B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	10/06/2010	n/a		
IB/0041	Change in the control of the drug substance 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	10/06/2010	n/a		

	material/intermediate				
II/0039	New site for the manufacture of the drug 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.	20/05/2010	01/06/2010		
IB/0040	Changes in the manufacture of the drug product B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	26/05/2010	n/a		
II/0036	Additional site for the manufacture of the drug substance. Change to the manufacturing process of the drug substance. Change(s) to the manufacturing process for the active substance	17/12/2009	25/01/2010	Annex II	
II/0038	Change to the drug product manufacturing process. Change(s) to the manufacturing process for the finished product	17/12/2009	07/01/2010		
II/0035	Update of section 5.3 of the SPC following completion of a long-term carcinogenicity study in rats.	22/10/2009	20/11/2009	SmPC and Labelling	Section 5.3 was updated to include a reference to the occurrence of malignant fibrous histiocytomas in males during a 2-year rat carcinogenicity study. The sentence read the package leaflet before use was deleted from the

	Update of Summary of Product Characteristics and Labelling				packaging to improve readability.
II/0037	Change to the storage conditions of the formulated drug substance Change(s) to shelf-life or storage conditions	22/10/2009	27/10/2009		
II/0033	Changes in the control of the drug substance Change(s) to the test method(s) and/or specifications for the active substance	24/09/2009	05/10/2009		
II/0034	Additional site for cell bank storage, release testing of the drug substance and stability testing of the drug substance and drug product. Change(s) to the manufacturing process for the active substance	23/07/2009	12/08/2009		
II/0031	Additional facility for Quality Control and stability testing of the drug substance and drug product Change(s) to the manufacturing process for the active substance	23/04/2009	08/05/2009		
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/03/2009	n/a	PL	
II/0029	Change to the purification process of the drug substance	18/12/2008	07/01/2009		

	Change(s) to the manufacturing process for the active substance				
II/0028	To introduce an additional rubber stopper for the immediate packaging of Somavert. Change(s) to the manufacturing process for the finished product	24/07/2008	29/07/2008		
II/0027	To extend the shelf life of the active substance. Change(s) to shelf-life or storage conditions	24/07/2008	29/07/2008		
IB/0025	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	28/05/2008	n/a	SmPC	
IA/0026	IA_09_Deletion of manufacturing site	21/05/2008	n/a	Annex II	
II/0023	Change(s) to the manufacturing process for the active substance	24/04/2008	05/05/2008		
II/0022	Quality changes	24/04/2008	05/05/2008		
II/0024	Change(s) to the manufacturing process for the finished product	19/03/2008	31/03/2008		
II/0021	Update of sections 4.2 and 4.8 of the Summary of Product Characteristics (SPC) and relevant sections of the Package Leaflet (PL) with respect to injection site reaction adverse events. The MAH took the opportunity to introduce one combined PL for all presentations and to update the contact number of	15/11/2007	21/12/2007	SmPC, Labelling and PL	In the assessment report of the Periodic Safety Update Report Number 6, the CHMP requested the MAH to submit a cumulative review of injection site reactions for Somavert. Based on this review, the MAH was requested to consider appropriate changes under the section 4.8 of the SPC, in particular with respect to "hypersensitivity,

	the Irish local representative in the section 6 of the PL. Some minor changes were also introduced in the set of Annexes. Update of Summary of Product Characteristics, Labelling and Package Leaflet				lipodystrophy/lipohypertrophy".The MAH therefore submitted a proposed wording for the section 4.2, 4.8 of the SPC and relevant sections of the PL with respect to injection site reaction adverse events. The following information was therefore included in the SPC: " Section 4.2 "Posology and Mehod of Administration": The site of injection should be rotated daily to help prevent lipohypertrophy. " Section 4.8 "Undesirable Effects": " General disorders and administration site conditions": Common: influenza-like illness, fatigue, injection site bruising or bleeding, injection site reaction (including injection site hypersensitivity), injection site hypertrophy (e.g. lipohypertrophy)*. The MAH took the opportunity to introduce one combined PL for all presentations and to update the contact number of the Irish local representative in the section 6 of the PL. Some minor changes were also introduced in the set of Annexes.
R/0020	Renewal of the marketing authorisation.	19/07/2007	20/09/2007	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit/risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Somavert continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity. Nevertheless, the MAH was requested to submit yearly PSUR for the next 3 years.

II/0017	Change(s) to the manufacturing process for the active substance	22/02/2007	28/02/2007		
II/0015	Change(s) to shelf-life or storage conditions	22/02/2007	28/02/2007		
IB/0019	IB_37_a_Change in the specification of the finished product - tightening of specification limits	07/02/2007	n/a		
II/0016	Change(s) to the test method(s) and/or specifications for the active substance	24/01/2007	31/01/2007		
II/0014	Change(s) to the manufacturing process for the active substance	24/01/2007	31/01/2007		
II/0012	Change(s) to the manufacturing process for the active substance	14/12/2005	20/12/2005		
II/0010	Change(s) to the manufacturing process for the active substance	17/11/2005	17/11/2005		
II/0009	Change(s) to the manufacturing process for the active substance	15/09/2005	15/11/2005	Annex II	
N/0011	The Marketing Authorisation Holder (MAH) applied to update the Package Leaflet in oder to reflect the use of the Mixject vial adapter as an alternative material to reconstitute the solution instead of using a needle through the rubber stopper. Additionnally the MAH updated the telephone numbers of the local representatives for Greece and Poland. Minor change in labelling or package leaflet not	11/11/2005	n/a	PL	

	connected with the SPC (Art. 61.3 Notification)				
II/0008	Change(s) to shelf-life or storage conditions	16/03/2005	21/03/2005		
IB/0007	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	31/01/2005	n/a	SmPC	
N/0006	The Marketing Authorisation Holder applied for changes to the labelling in order to comply with the latest QRD guidelines and for changes to the list of local representatives. In addition the MAH corrected typographical errors. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/01/2005	n/a	Labelling and PL	
II/0004	Quality changes	23/06/2004	04/08/2004	Annex II and PL	
IA/0005	IA_05_Change in the name and/or address of a manufacturer of the finished product	27/07/2004	n/a		
T/0003	Transfer of Marketing Authorisation for Somavert from Pharmacia Enterprises S.A. to Pfizer Limited. Transfer of Marketing Authorisation	27/08/2003	20/10/2003	SmPC, Labelling and PL	
I/0002	30_Change in pack size for a medicinal product	31/07/2003	16/09/2003	SmPC, Labelling and PL	
II/0001	Change(s) to the manufacturing process for the active substance	22/05/2003	18/08/2003	SmPC, Labelling and	

				PL	