Revatio

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
IAIN/0111	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	22/04/2024		SmPC and PL	

[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).

IG/1692/G	This was an application for a group of variations. B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition) 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	12/01/2024		Annex II and PL	
WS/2475/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.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.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	11/01/2024	n/a		

	material/intermediate				
II/0107	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	30/11/2023	n/a		
IG/1672/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.1.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)	05/10/2023	n/a		
N/0106	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/09/2023		PL	
WS/2516	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	31/08/2023	n/a		

	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				
N/0104	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/03/2023	24/04/2023	PL	
IG/1545/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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	27/09/2022	n/a		
N/0102	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/07/2022	24/04/2023	PL	
II/0098	Update of Sections 4.8 and 5.1 to include long-term safety data in adults for the approved dose, and evidence of safe and effective use in adults in higher than recommended doses, based on Study A1481324; a multinational, multicentre randomised, double-blind, parallel-group study in 385 adults with Pulmonary Arterial Hypertension (PAH) undertaken to assess the effects of different dose levels of oral sildenafil on mortality. In addition, the MAH took the opportunity to implement editorial changes in the	28/04/2022	24/04/2023	SmPC, Labelling and PL	SmPC new text Update of sections 4.8 and 5.1 of the SmPC to add the information on safety data for sildenafil 5 mg TID (4 times lower than the recommended dose), 20 mg TID (recommended dose) and 80 mg TID (4 times the recommended dose), based on the A1481324 study, a Phase 3B/4, multinational, multicentre, randomised, double-blind, parallel-group study in 385 adults with PAH to investigate the effects of three different dose levels of sildenafil on mortality. Patients were randomly assigned

	SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				1:1:1 to one of three dosage groups (5 mg TID (4 times lower than the recommended dose), 20 mg TID (recommended dose) and 80 mg (4 times the recommended dose)). In total, the majority of subjects were PAH treatment naïve (83.4%). For most subjects the etiology of PAH was idiopathic (71.7%). The most common WHO Functional Class was Class III (57.7% of subjects). All three treatment groups were well balanced with respect to baseline demographics of strata history of PAH-treatment and etiology of PAH, as well as the WHO Functional Class categories. The mortality rates were 26.4% (n=34) for the 5 mg TID dose, 19.5% (n=25) for the 20 mg TID dose and 14.8% (n=19) with the 80 mg TID dose. Overall, the safety data for sildenafil 20 mg TID (recommended dose) and for sildenafil 80 mg TID (4 times the recommended dose), were consistent with the established safety profile of sildenafil in previous adult PAH studies. For more information, please refer to the Summary of Product Characteristics.
PSUSA/2700/ 202105	Periodic Safety Update EU Single assessment - sildenafil (indicated for pulmonary hypertension)	27/01/2022	01/04/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2700/202105.
N/0101	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/03/2022	24/04/2023	PL	
N/0100	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/12/2021	01/04/2022	PL	
IAIN/0099	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is	17/11/2021	n/a		

	not an integrated part of the primary packaging - Device with CE marking				
N/0097	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/10/2021	15/11/2021	PL	
N/0095	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2021	15/11/2021	PL	
II/0091	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	10/06/2021		Annex II	
IA/0094	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	30/03/2021	n/a		
IB/0092	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/11/2020	15/11/2021	SmPC, Annex II, Labelling and PL	
IAIN/0093	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	04/11/2020	n/a		
II/0090/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	23/07/2020	n/a		

	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 A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.I.z - Quality change - Active substance - Other variation				
T/0089	Transfer of Marketing Authorisation	03/04/2020	02/06/2020	SmPC, Labelling and PL	
II/0086	Update of sections 4.2 and 5.1 of the SmPC based on the final results from study A1481316; this is a multi-centre, randomised, placebo-controlled, double-blind, two-armed, parallel group study to evaluate efficacy and safety of iv sildenafil in the treatment of neonates with persistent pulmonary hypertension of the newborn (PPHN) or hypoxic respiratory failure and at risk for PPHN, with a long-term follow-up investigation of developmental progress 12 and 24 months after completion of study treatment. In addition some minor editorial updates to the Product Information are being proposed. The applicant also took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	27/02/2020	02/06/2020	SmPC, Labelling and PL	Sildenafil should not be used in neonates with persistent pulmonary hypertension of the newborn (PPHN). Results from a placebo-controlled clinical trial in neonates with PPHN, or hypoxic respiratory failure and at risk for PPHN did not show statistically significant differences on treatment failure rates, defined as need for additional treatment targeting PPHN, the need for extracorporeal membrane oxygenation, or death between the two treatment arms.

	data				
WS/1741	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	16/01/2020	n/a		
N/0088	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/11/2019	02/06/2020	PL	
WS/1464/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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 A.7 - Administrative change - Deletion of manufacturing sites B.I.z - Quality change - Active substance - Other variation	23/05/2019	n/a		
N/0085	Minor change in labelling or package leaflet not	21/05/2019	02/06/2020	PL	

	connected with the SPC (Art. 61.3 Notification)				
PSUSA/2700/ 201805	Periodic Safety Update EU Single assessment - sildenafil (indicated for pulmonary hypertension)	17/01/2019	n/a		PRAC Recommendation - maintenance
T/0082	Transfer of Marketing Authorisation	11/07/2018	30/07/2018	SmPC, Labelling and PL	
N/0080	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/04/2018	30/07/2018	Labelling	
IAIN/0081	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	27/02/2018	n/a		
IA/0079/G	This was an application for a group of variations. B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised	25/01/2018	n/a		
IA/0078/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.a - Change in the manufacturing process of	08/12/2017	n/a		

	the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				
II/0077	Update of section 4.6 of the SmPC in order to revise the statement concerning the detection of sildenafil and its active metabolite in human milk and the potential for impact on the breastfed infant. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/10/2017	30/07/2018	SmPC, Labelling and PL	There are no adequate and well controlled studies in lactating women. Based on data from one lactating woman, it has been concluded that sildenafil and its active metabolite N-desmethylsildenafil are excreted into breast milk at very low levels. No clinical data are available regarding adverse events in breast-fed infants, but amounts ingested would not be expected to cause any adverse effects. Prescribers should carefully assess the mother's clinical need for sildenafil and any potential adverse effects on the breast-fed child.
IAIN/0076	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	25/11/2016	10/11/2017	SmPC, Labelling and PL	
II/0073	Following the availability of powder for oral suspension formulation and following the request of CHMP, update of sections 4.2, 6.3, 6.4 and 6.6 of Revatio 20mg film-coated tablets SmPC and section 4.2 of Revatio 10mg powder for oral suspension to delete information related to the extemporaneously prepared oral suspension. The film-coated tablet PL	23/06/2016	29/07/2016	SmPC and PL	

	is updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
N/0075	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/06/2016	29/07/2016	PL	
IB/0074/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	07/06/2016	n/a		
IB/0072	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	29/04/2016	n/a		
PSUSA/2700/ 201505	Periodic Safety Update EU Single assessment - sildenafil (indicated for pulmonary hypertension)	14/01/2016	n/a		PRAC Recommendation - maintenance
IAIN/0071	B.II.a.3.a.1 - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Addition , deletion or replacement	04/12/2015	31/03/2016	SmPC and PL	
IB/0070	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/10/2015	31/03/2016	SmPC, Annex II, Labelling	

				and PL	
N/0068	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	31/03/2016	PL	
IB/0067	B.II.e.5.2 (type IB) - To add a new pack size of 300 tablets in blisters (PVC/Alu) for the Revatio 20 mg film-coated tablets presentation (EU/1/05/318/004). In addition the MAH is introducing a correction in the section 3 of the PIL for the Bulgarian language for the 20 mg film-coated tablets. B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	09/04/2015	31/03/2016	SmPC, Labelling and PL	
IB/0066	B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits	26/03/2015	n/a		
PSUV/0063	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
IAIN/0065	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	23/10/2014	17/11/2014	Annex II and PL	
II/0062	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	17/11/2014	SmPC and PL	

II/0061	Update of the RMP to version 6.1. The MAH also took the opportunity to update Annex II to remove information on the switch from the 50 ml vial to the 20 ml vial for Revatio 0.8 mg/ml solution from the key elements included in the Information for Healthcare Professionals and to delete the obligation to submit study A1481243. 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	25/09/2014	17/11/2014	Annex II	The updated RMP version 6.1 is acceptable. In addition, it is agreed to remove information on the switch from the 50 ml vial to the 20 ml vial for Revatio 0.8 mg/ml solution from the key elements included in the Information for Healthcare Professionals in Annex II.D since the 50 ml vial size is no longer marketed. Furthermore, the obligation to conduct the post-authorisation measure regarding study A1481243 has been removed from Annex II D, as this obligation has been fullfilled.
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/09/2014	17/11/2014	PL	
II/0060	Update of sections 4.4 and 4.5 of the SmPC . A warning in Package leaflet is introduced accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/05/2014	17/11/2014	SmPC and PL	This variation introduced • Addition of a warning regarding priapism and prolonged erection under Section 4.4 Special warnings and precautions for use of the SmPC • Addition of information regarding concomitant use of sildenafil citrate with other phosphodiesterase type–5 (PDE5) inhibitors under Section 4.4 Special warnings and precautions for use • Update to the description of erythromycin as a moderate rather than a specific CYP3A4 inhibitor in Section 4.5 Interaction with other medicinal products and other forms of interaction.

PSUV/0058	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
II/0056	Update of sections 4.2, 4.4, 4.5 and 5.1 of the SmPC based on the results of study A1481243 in order to: - include a warning on the concomitant use of sildenafil with bosentan (section 4.4) - reflect the drug-drug interaction data on the concomitant use of sildenafil with bosentan (section 4.5) - describe the relevant efficacy results of study A1481243 (section 5.1) A minor editorial change is also introduced in section 4.2. In addition, an update of the Annex II is adopted to remove the requirement to complete the study A1481243 by June 2013. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2013	17/11/2014	SmPC and Annex II	The MAH submitted results of the A1481243 study, a randomised double-blind, placebo-controlled study of sildenafil (20 mg TID) or placebo added to stable background bosentan therapy (62.5–125 mg twice daily [BID]) in adults with PAH. This study was designed to evaluate the efficacy, safety and clinical relevance of concomitant therapy given the PK interaction between sildenafil and bosentan. It is acknowledged that the results of this study are not generalisable to the clinical setting where use of sequential combination therapy is currently recommended by international PAH guidelines; that is, when clinical response to initial monotherapy is inadequate.
IA/0059	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	11/12/2013	n/a		
II/0057	The MAH proposed the update of sections 4.8 and 5.1 of the SmPC following submission of the final study report of study 1481156 (extension study) in the paediatric population.	21/11/2013	17/11/2014	SmPC and PL	Update of sections 4.8 and 5.1 of the SmPC following submission of the final study report of study 1481156 (extension study) in the paediatric population. The Package leaflet is updated accordingly.

	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				Summary of the 1481156 long term extension study Of the 234 paediatric subjects treated in the short-term, placebo-controlled study, 220 subjects entered the long-term extension study. Subjects who had been in the placebo group in the short-term study were randomly reassigned to sildenafil treatment; subjects weighing ≤ 20 kg entered the medium or high dose groups (1:1), while subjects weighing > 20 kg entered the low, medium or high dose groups (1:1:1). Of the total 229 subjects who received sildenafil, there were 55, 74, and 100 subjects in the low, medium and high dose groups, respectively. Across the short-term and long-term studies, the overall duration of treatment from start of double-blind for individual subjects ranged from 3 to 3129 days. By sildenafil treatment group, median duration of sildenafil treatment was 1696 days. Kaplan-Meier estimates of survival at 3 years, in patients > 20 kg in weight at baseline, were 942 %, 930 % and 854 % in the low, medium and high dose groups, respectively; for patients ≤ 20 kg in weight at baseline, the survival estimates were 943 % and 934 % for subjects in the medium and high dose groups respectively. During the conduct of the study, there were a total of 42 deaths reported, whether on treatment or reported as part of the survival follow-up. 37 deaths occurred prior to a decision taken by the Data Monitoring Committee to down titrate subjects to a lower dosage, based on an observed mortality imbalance with increasing sildenafil doses. Among these 37 deaths, the number (%) of deaths was 5/55 (9.1%), 10/74 (13.5%), and 22/100 (22%) in the sildenafil

					low, medium, and high dose groups, respectively. An additional 5 deaths (were reported subsequently. The causes of deaths were related to PAH. Higher than recommended doses should not be used in paediatric patients with PAH. The most common adverse reactions reported across the duration of the short-term and long-term studies were generally similar to those observed in the short-term study. Adverse reactions reported in >10% of 229 subjects treated with sildenafil (combined dose group, including 9 patients that did not continue into the long-term study) were upper respiratory infection (31%), headache (26%), vomiting (22%), bronchitis (20%), pharyngitis (18%), pyrexia (17%), diarrhoea (15%), and influenza, epistaxis (12% each). Most of these adverse reactions were considered mild to moderate in severity.
II/0055	Update of section 4.8 of the SmPC and package leaflet in order to : - amend the sub-section related to the paediatric information and include additional adverse reactions (upper respiratory infection, bronchitis, pharyngitis, pneumonia, rhinorrhoea and rhinitis) following a recent update of the Core Data Sheet. - amend terms (blood shot eyes/red eyes, blurred vision, sudden deafness, skin rash, limb pain and prolonged erection) to the latest MEdDRA terminology. - re-categorise terms (vomiting, pyrexia, nausea, increased erection and spontaneous penile erections) previously included in section 4.8 of the SmPC as treatment related adverse events and now	19/09/2013	13/12/2013	SmPC and PL	Revision of existing Adverse Drug Reactions (ADR) terms The MAH reviewed some Adverse Drug Reactions using the MedDRA dictionary to determine if the term currently being used in the SmPC were MedDRA Preferred Terms. Some ADRs required revisions to their corresponding MedDRA PT specifically Bloodshot eyes/red eyes, Blurred vision, and Limb pain. They were changed to Ocular hyperaemia, Vision blurred, and Pain in extremity, respectively. In addition Sudden deafness, Skin rash, and Prolonged erection were changed to Sudden hearing loss, Rash, and Erection increased, respectively. The lower level term "non-arteritic anterior ischaemic optic neuropathy (NAION)" was retained, however, in order to ensure consistency. Review of Adverse Drug Reactions (ADR) in the paediatric

	considered as adverse drug reactions. The package leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				study A1481131 The MAH made a review of treatment-related adverse events observed during Study A1481131 (Paediatric study) that occurred with a frequency ≥1% in Revatio patients (combined doses) and with a frequency > 1 % over placebo patients. A further analysis has been conducted to determine which of the events reported during the study are considered to represent Adverse Drug Reactions to the product. Based on this review an amendment of section 4.8 is introduced.
N/0054	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/07/2013	13/12/2013	PL	
II/0053	Update of SmPC, annex II, labelling and package leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/07/2013	13/12/2013	SmPC, Annex II, Labelling and PL	Update of Sections 4.4 and 4.8 of the Summary of Product Characteristics in order to add a warning related to the results of Study A1481259 suggesting an increase in the risk of NAION with PDE5 inhibitor use and introduce minor modification in the adverse event section. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and propose minor corrections to the PI. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.
II/0051/G	This was an application for a group of variations. This was an application for a group of variations: - To add an alternative manufacturing process of the active substance. - To add new specification parameters to the	30/05/2013	n/a		

	specifications of an intermediate used in the manufacturing process of the active substance. - To add a new test procedure for starting materials and intermediates used in the manufacturing process of the active substance. - To change the specifications parameters of the active substance. - To change the test procedures for the active substance. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product 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.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.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.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				
IB/0052/G	This was an application for a group of variations. 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.2.z - Change in test procedure for the finished product - Other variation B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	19/03/2013	n/a		
II/0048	Update of sections 4.8 of the SmPC in order to update the safety information as a class labelling for PDE5 inhibitors as required by the CHMP FUM 037, following assessment of safety signal of penile heamorrage for PDE5 inhibitors. The Package Leaflet was updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.3.z - Implementation of change(s) requested	13/12/2012	13/12/2013	SmPC and PL	The assessment of the data concerning background incidence, literature, clinical trials, post-marketing experience, and data mining leads to the following conclusion: Inclusion of the terms Penile haemorrhage, Haematospermia, and Haematuria to Section 4.8 of the sildenafil (Revatio) SmPC with a frequency of uncommon (based on clinical trial data) is considered acceptable. The Package leaflet is updated accordingly.

	following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation				
IG/0235/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	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
IA/0049	B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction	23/10/2012	n/a		
II/0044	Update of sections 4.8 and 5.1 of the SmPC in order to provide the prescriber with updated data regarding the use of sildenafil in doses higher than the approved dose recommended dose of 20 mg three times a day (TID) in adults with pulmonary arterial hypertension (PAH). In addition minor updates of the package leaflet are introduced to bring in line the information mentioned in both tablets and IV formulations. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	27/06/2012	SmPC, Labelling and PL	Based on review of available evidence of use of Revatio in adult PAH patients at doses higher than the recommended dose of 20 mg three times a day, updated information is introduced in sections 4.8 and 5.1. In particular, description of the results observed on efficacy haemodynamic endpoints is introduced in section 5.1 for doses up to 40mg and 80 mg three times a day. Long term survival data in a epoprostenol add on therapy study is introduced for adults patients.
IG/0169/G	This was an application for a group of variations.	08/06/2012	n/a		

	C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IB/0046	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	31/05/2012	n/a		
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/05/2012	27/06/2012	Labelling	
II/0040	Update of sections 4.4 and 4.8 of the SmPC. In addition an updated RMP was submitted as part of this application. 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	15/03/2012	13/04/2012	SmPC	Update of section 4.4 of the SmPC following CHMP request in order to add a section regarding the potential for vaso-occlusive crises occurring in patients being treated for pulmonary hypertension secondary to sickle cell anaemia. The following amendment was approved: Section 4.4 Vaso-occlusive crises in patients with sickle cell anaemia Sildenafil should not be used in patients with pulmonary hypertension secondary to sickle cell anaemia. In a clinical study events of vaso-occlusive crises requiring hospitalisation were reported more commonly by patients

					receiving Revatio than those receiving placebo leading to the premature termination of this study In addition, an update of section 4.8 of the SmPC was introduced to bring the section in line the MEdDRA SOC terminology.
X/0037	To add a new pharmaceutical form: Revatio 10 mg/ml powder for oral suspension Annex I_2.(d) Change or addition of a new pharmaceutical form Annex I_2.(c) Change or addition of a new strength/potency	19/01/2012	21/03/2012	SmPC, Labelling and PL	
IB/0042	B.II.a.z - Change in description and composition of the Finished Product - Other variation	11/01/2012	21/03/2012	SmPC and PL	
II/0041	Update of SPC and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/09/2011	24/10/2011	SmPC and PL	Based on the request of CHMP following deaths related to an ongoing paediatric study and corresponding Data Monitoring Board recommendations a type II variation to update sections 4.2, 4.4 and 5.1 of the Summary of Product Characteristics has been adopted. Updated information has been added to highlight that in paediatric patients, doses higher than the recommended doses should not be used. Corresponding changes in the Package Leaflet have been adopted. A DHPC letter was also discussed and endorsed as part of this variation. This variation concerns the oral tablet formulation only.
N/0038	Minor change in labelling or package leaflet not	18/10/2011	n/a	PL	

	connected with the SPC (Art. 61.3 Notification)				
IA/0043	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	12/10/2011	n/a		
IA/0039	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	10/08/2011	n/a		
II/0028	Update of Summary of Product Characteristics, annex II, labelling and Package Leaflet to introduce a new indication in paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. The above extension of indication applies to the oral tablet formulation only. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	17/03/2011	02/05/2011	SmPC, Annex II, Labelling and PL	This application is based on quality and clinical data. The paediatric studies including clinical pharmacology data pertinent to this submission are Studies A1481134 and A1481157 with intravenous sildenafil in PAH (supportive for clinical pharmacology and safety data) and pivotal study A1481131 for PK/PD data with oral sildenafil, establishing population PK and PK-PD models, and driving the oral dose recommendation for the paediatric population. Interim data of study A1481156, the long term extension of study A1481131 are also supporting this application. It is concluded that efficacy data based on improvement of exercise capacity or pulmonary haemodynamics support an indication for the treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease. The granted indication is as follows: Paediatric population

					Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease. The granted indication concerns only the oral tablet pharmaceutical formation. The approval of this suspension for extemporaneous formulation is an interim measure temporally accepted. The MAH has committed to develop a suitable age appropriate formulation in a form of a powder for oral suspension (POS) which is currently under development. In addition, minor amendments are introduced in the product information for both tablets and IV formulation based on QRD comments received from the renewal application.
II/0035	Update of SPC section 4.8 and update of Package Leaflet accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/02/2011	24/03/2011	SmPC and PL	Following the request by CHMP/EMA, the MAH has applied to update section 4.8 to include the term "hypotension" with a frequency "unknown". The Package Leaflet has been updated accordingly.
IG/0044/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the	02/03/2011	n/a	Annex II	

	DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IB/0036	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	07/02/2011	n/a		
II/0030/G	This was an application for a group of variations. B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, and biological/immunological multidose parenteral medicinal products B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	21/10/2010	21/01/2011	SmPC, Annex II, Labelling and PL	To change the vial size of Revatio solution for injection (EU/1/05/318/002) from 50 ml to 20 ml and to reduce the fill volume to 12.5 ml. In addition, the Annex II was revised for the 20ml vial.
II/0029	Update of Section 5.1 of the SPC to include data on time to clinical worsening. The list of local representatives has also been updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/10/2010	21/01/2011	SmPC and PL	Update of section 5.1 of the SPC to include data relating the time to clinical worsening when Revatio is administered in patients stabilized on epoprostenol. The data is derived from study A1481141 that was previously assessed in 2006, and its main results (6-MWT and hemodynamics) are already incorporated in section 5.1. The data on time to clinical worsening is considered to date as relevant to

					current clinical practice as shown in the REVEAL study and the ESC guideline. The sildenafil dose used in this study (80 mg TID) is higher than that currently approved (20 mg TID); however this is clearly described in section 5.1.
R/0032	Renewal of the marketing authorisation.	22/07/2010	23/09/2010	SmPC and PL	The CHMP is of the opinion that the quality, safety and efficacy continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Revatio is favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity. Amendments of sections 4.2, 4.3 and 4.5 of the SPC are introduced to align the CYP3A4 inhibitor terminology used with current classification standards for CYP3A4.
II/0031	Update of sections 6.2 and 6.6 of the Summary of Product Characteristics (SmPC) to include diluent compatibility data for Revatio solution for injection. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/07/2010	26/08/2010	SmPC	
IB/0027	IB_27_b_Change to test proc. of immediate packaging - other changes (incl. replacement/addition)	29/01/2010	n/a		
X/0019	Addition of a new pharmaceutical form, strength and route of administration. Annex I_2.(d) Change or addition of a new pharmaceutical form	24/09/2009	21/12/2009	SmPC, Annex II, Labelling and PL	The Marketing Authorisation Holder submitted an extension application for a new pharmaceutical form, strength and route of administration: Revatio 0.8 mg/ml, solution for injection.

					Revatio 0.8 mg/ml, solution for injection is indicated for the treatment of patients with pulmonary arterial hypertension who are currently prescribed oral Revatio and who are temporarily unable to take oral medicine, but are otherwise clinically and haemodynamically stable. Revatio (oral) is indicated for treatment of patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease. Please refer to Scientific Discussion Revatio-H-C-638-X-19.
II/0023	Update of DDPS (Pharmacovigilance)	25/06/2009	03/08/2009	Annex II	The Detailed Description of the Pharmacovigilance System (DDPS) has been updated (version 2.0) in order to reflect various organisational changes as well as the change of the global safety database. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
II/0021	Extension of Indication	29/05/2009	07/07/2009	SmPC	Extension of indication in patients with Pulmonary Arterial Hypertension classified as WHO functional class II. Consequently, sections 4.1 and 5.1 of the SPC have been updated. Minor editorial changes were also made to the SPC. Please refer to Scientific Discussion Revatio: H-638-II-21-AR.
IB/0026	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	27/05/2009	n/a		

IA/0025	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	05/05/2009	n/a		
IA/0024	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	05/05/2009	n/a		
IA/0022	IA_09_Deletion of manufacturing site	05/03/2009	n/a		
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/02/2009	n/a	PL	
II/0018	Update of Detailed Description of the Pharmacovigilance System Update of DDPS (Pharmacovigilance)	25/09/2008	28/10/2008	Annex II	The Marketing Authorisation Holder applied to update the Detailed Description of the Pharmacovigilance System (DDPS). Consequently, Annex II has been updated using standard text including the numbers of the version agreed for the DDPS (version 1.1) and for the Risk Management Plan (version 2.1).
S/0017	Annual re-assessment.	30/05/2008	25/08/2008	SmPC, Annex II, Labelling and PL	As part of the initial MA, the MAH had agreed to comply with the following remaining Specific Obligations to extend the ongoing studies A1481142 (sildenafil only) and A1481153 (sildenafil-epoprostenol) to obtain further data on mortality with long-term sildenafil use in PAH patients. Study A1481142 was completed and submitted to the CHMP. Study A1481142 was a long-term extension study to assess the safety and tolerability of optimized treatment regimens of oral sildenafil for PAH in subjects who have completed study A1481140 (pivotal study in the initial marketing authorisation application). Based on the submitted results, the CHMP considers that there is no suggestion of an increased mortality risk. The majority of adverse events in this study were consistent with the

					known safety profile of sildenafil as no new safety risks were identified. Study A1481153 is a long-term, open-label extension study to assess the safety of optimized treatment regimens of oral sildenafil when used in combination with epoprostenol, for PAH subjects who have completed study A1481141 (pivotal study in the initial marketing authorisation application). This study is still on-going; Interim results were provided as part of this 2nd annual re-assessment application. The safety data from these interim results further support the results of Study A1481142. Additional results from this long-term extension study are not expected to influence this profile. In addition, post marketing experience as reported in the PSURs since the first annual re-assessment continue to support the overall favourable benefit/risk profile for Revatio. The CHMP agreed for the remaining specific obligation is changed into a follow-up measure making provision of Study A1481153 final data a standard clinical FUM. Based on the available data, the CHMP considered this proposal to be acceptable and that there are no grounds for the Marketing Authorisation to remain under exceptional circumstances. The SPC, Anne
II/0016	Update of section 4.8 of the SPC and section 4 of the Package Leaflet with the adverse reaction "sudden deafness/hearing loss" with a frequency not known, upon request from the CHMP following a review of clinical and post-marketing adverse reactions with	21/02/2008	17/03/2008	SmPC and PL	Following post-marketing case reports, the CHMP performed a review of clinical and post-marketing adverse reactions of sudden deafness/hearing loss with PDE5 inhibitors. Data from placebo controlled trials revealed a low incidence

	PDE5 inhibitors. In addition, the MAH took the opportunity to make linguistic changes to the Product Information Update of Summary of Product Characteristics and Package Leaflet				for deafness/hearing impairment events in sildenafil treated patients. Based on the current data available, there is insufficient evidence of a causal relationship between the use of sildenafil and hearing loss. Nevertheless, the CHMP considered that 'sudden deafness' should be added to section 4.8 with a frequency 'not known' for the PDE5 inhibitors with the sentence "Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil" as a footnote. The Package Leaflet has been amended accordingly to include the sentence "Sudden decrease or loss of hearing has been reported." In addition, the MAH took the opportunity to make linguistic changes to the Product Information
IB/0015	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	09/11/2007	n/a		
IA/0014	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) Update of Summary of Product Characteristics and Package Leaflet	16/10/2007	n/a		
IA/0013	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	15/10/2007	n/a		
IA/0012	IA_13_a_Change in test proc. for active substance - minor change IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	19/09/2007	n/a		

IA/0011	IA_13_a_Change in test proc. for active substance - minor change IA_20_a_Change in test procedure for an excipient - minor change to approved test procedure	19/09/2007	n/a		
IA/0010	IA_13_a_Change in test proc. for active substance - minor change IA_20_a_Change in test procedure for an excipient - minor change to approved test procedure	19/09/2007	n/a		
N/0009	The MAH has applied to update the contact details for LV and SK in the list of local representatives in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/08/2007	n/a	PL	
IA/0008	IA_13_a_Change in test proc. for active substance - minor change	05/07/2007	n/a		
N/0007	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/05/2007	n/a	PL	
S/0005	Annual re-assessment.	22/02/2007	13/04/2007	Annex II	Annual Re-Assessment of specific obligation and follow-up measure.
II/0006	Update of Summary of Product Characteristics and Package Leaflet	22/02/2007	29/03/2007	SmPC and PL	The MAH applied for a type II variation, upon request by the CHMP, to include "prolonged erection" and "priapism" as adverse drug reactions in section 4.8 of the SPC. The Package Leaflet has been updated accordingly. In addition, the MAH proposed the update of the frequency

					of ocular post-marketing adverse events in the Package Leaflet to bring it in line with section 4.8 of the SPC.
II/0003	Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	17/01/2007	SmPC and PL	The MAH has submitted the results of a combination study sildenafil-epoprostenol (study A1481141), to fulfil a FUM agreed at the time of the initial MA. As a consequence, the MAH has applied to update Sections 4.2, 4.8 and 5.1 of the SPC. The Package Leaflet has been updated accordingly. The MAH has also taken the opportunity to update to the latest QRD template (7.2).
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/10/2006	n/a	PL	
II/0002	Update of Summary of Product Characteristics (Section 4.8 undesirable effects) and the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	28/08/2006	SmPC and PL	Addition of skin rash (frequency unknown) under skin and subcutaneous tissue disorders in the SPC.
II/0001	Update of Summary of Product Characteristics, Labelling and Package Leaflet	27/04/2006	16/06/2006	SmPC, Annex II, Labelling and PL	The MAH applied for an update of section 4.2, 4.3, 4.4 and 4.8 of the SPC. The update corresponds to the implementation of the class review for PDE5 inhibitors regarding NAION cases and also to an update of information regarding sildenafil-bosentan administration further to a previous CHMP request. The Package Leaflet has been updated accordingly. The whole product information was amended to reflect changes according to the new legislation.