Ventavis

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
N/0072	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/11/2023		PL	
IB/0071/G	This was an application for a group of variations. B.I.b.2.c - Change in test procedure for AS or	07/09/2022	n/a		

[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).

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	starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
IB/0070	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	23/08/2022	n/a		
N/0069	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2021		PL	
PSUSA/1724/ 202009	Periodic Safety Update EU Single assessment - iloprost (nebuliser solution only)	06/05/2021	n/a		PRAC Recommendation - maintenance
IB/0067/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	18/12/2020		SmPC, Annex II, Labelling and PL	
II/0066	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	29/10/2020	n/a		

IA/0065/G	This was an application for a group of variations. B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)	20/12/2019	n/a		
IAIN/0064	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	11/12/2019	n/a		
IB/0063/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.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	01/10/2019	n/a		
IB/0062	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale	06/09/2019	13/02/2020	SmPC	

	(supported by real time data)				
IB/0061	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/02/2019	13/02/2020	SmPC and PL	
IA/0060	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	24/10/2018	n/a		
PSUSA/1724/ 201709	Periodic Safety Update EU Single assessment - iloprost (nebuliser solution only)	17/05/2018	n/a		PRAC Recommendation - maintenance
T/0059	Transfer of Marketing Authorisation	24/01/2018	09/02/2018	SmPC, Labelling and PL	
IA/0057	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	21/12/2017	n/a		
IB/0056/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.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a	24/10/2017	n/a		

	non-significant specification parameter				
II/0055	Update of sections 4.9 of the SmPC in order to update the safety information related to overdose following a cumulative review of overdose cases. The Package Leaflet (PIL) is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the PIL, to align the PIL with the SmPC for children and adolescents and to adjust the labelling of the inner carton without blue box. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/06/2017	11/09/2017	SmPC, Labelling and PL	The SmPC is updated with the below: 4.9 Overdose Symptoms Cases of overdose were reported. Symptoms of overdoses are mainly related to the vasodilatory effect of iloprost. Frequently observed symptoms following overdose are dizziness, headache, flushing, nausea, jaw pain or back pain. Hypotension, an increase of blood pressure, bradycardia or tachycardia, vomiting, diarrhoea and limb pain might also be possible.
IA/0054	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	20/02/2017	n/a		
II/0051/G	This was an application for a group of variations. Grouped application to introduce the new additional nebulizer FOX Bavent, the name of which has been changed by the MAH to BREELIB for application of Ventavis 10 µg/ mL and Ventavis 20 µg/mL, nebulizer solution: - Type IB variation to add the additional nebulizer; - Type IAIN variation for change of pack sizes within the range of current approved pack sizes; - Type II variation to implement consequential	13/10/2016	11/09/2017	SmPC, Annex II, Labelling and PL	N/A

	changes to SmPC sections 4.2, 4.4, 5.2, 5.3, 6.5 and 8, as well as to the Labelling and Package Leaflet. In addition, the MAH took the opportunity to delete reference in the product information to nebulizers which are no longer available by the device manufacturer (ProDose and HaloLite), to merge the texts for Ventavis 10 µg/ mL and Ventavis 20 µg/ mL nebulizer solution into one SmPC and one Package Leaflet text, to update the list of local representatives in the Package Leaflet, to implement minor editorial changes in the annexes and to bring the annexes in line with the latest QRD template version 9.1. An updated RMP version 7.1 was agreed during the procedure. 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.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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0052/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites	02/06/2016	n/a		

	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 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.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier 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.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.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation				

PSUSA/1724/201409	Periodic Safety Update EU Single assessment - iloprost (nebuliser solution only)	10/04/2015	n/a		PRAC Recommendation - maintenance
IAIN/0049	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	06/11/2014	03/11/2015	SmPC, Labelling and PL	
IAIN/0048	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	06/11/2014	03/11/2015	SmPC, Labelling and PL	
II/0047/G	This was an application for a group of variations. Change in the manufacturing process of the finished product. Change in the batch size (including batch size ranges) of the finished product. B.II.b.3.e - Change in the manufacturing process of the finished or intermediate product - Introduction or increase in the overage that is used for the AS B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation	25/09/2014	n/a		
X/0043	Line extension application to add a new strength: the 20 microgram/ml nebuliser solution. Annex I_2.(c) Change or addition of a new	22/05/2014	18/07/2014	SmPC, Annex II, Labelling and PL	Please refer to the assessment report Ventavis-H-C-474-X-43-AR.

	strength/potency				
IA/0046	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/04/2014	n/a		
PSUV/0045	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
II/0044	Update of section 4.2 and 4.8 of the SmPC in order to align the product information with the Company Core Data Sheet. The Package Leaflet was updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 9.0 and changes have been made throughout the SmPC to align with the SmPC guideline The requested variation proposed amendments to the Summary of Product Characteristics, 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	21/11/2013	18/07/2014	SmPC, Annex II, Labelling and PL	The MAH provided a safety review of palpitation, tachycardia, peripheral oedema and nasal congestion in view to add these adverse events in the section 4.8 of the SmPC. Causality of iloprost in reported post marketing cases of tachycardia and palpitations is not clear. However, the role of iloprost, as a vasodilator, cannot be excluded. The CHMP therefore agreed to adding tachycardia and palpitations in the section 4.8 of the SmPC with a frequency of "common". With regards to peripheral oedema, even if a possible pharmacologic mechanism is suggested, the CHMP considers that the data provided do not allow to clearly establishing a relationship between the occurrence of peripheral oedema, and the statement currently in the SmPC is considered appropriate with no changes warranted. The CHMP did agree however to the inclusion of peripheral oedema in section 4.8. with a frequency of "very common", as even if the data provided does not allow to establish a clear relationship between the occurrence of peripheral oedema it is a fact that the role of iloprost cannot be formally excluded Regarding "nasal congestion", the current data provided do not allow to clearly establishing a relationship, therefore

					this ADR has not been included in section 4.8 of the SmPC. In addition to these changes, during the procedure the CHMP commented that given the available data and the very limited treatment alternatives for paediatric patients with PAH that is a life threatening disease, it would be counterproductive and confusing to the prescriber and patient to introduce a recommendation against the use of Ventavis in adolescents and paediatric patients. In addition to this the statement is not in line with the SmPC guideline. In light of these considerations the statement "Ventavis is not recommended for use in this population" was to be deleted from section 4.2 of the SmPC, and the package leaflet amended accordingly. This review does not change the benefit/risk balance.
R/0042	Renewal of the marketing authorisation.	30/05/2013	26/08/2013	SmPC, Annex II, Labelling and PL	Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considers by consensus that the risk-benefit balance of Ventavis in the treatment of primary pulmonary arterial hypertension remains favourable. The CHMP also concludes that the specific obligation to conduct a post-authorisation safety study to assess the clinical effects, safety and tolerability, and survival during long-term Ventavis inhalation therapy over at least 2 years and up to 4 years in a usual care setting had been fulfilled. The efficacy data from this study support results from randomised clinical trials and the observed safety profile for Ventavis in this study was expected and in line with information mentioned in the current label. No safety signal emerged from this observational study. In view of these results the CHMP recommends the renewal of the

					marketing authorisation and since all specific obligations have been fulfilled, there are no remaining grounds for the Marketing Authorisation to remain under exceptional circumstances.
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/12/2012	26/08/2013	Labelling and PL	
II/0038/G	This was an application for a group of variations. Update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.2 and 5.3 of the SmPC to: - update the effect of vasodilatators and antihypertensive agents further to the assessment of FU2 026.2 (section 4.5). - amend the posology section and update the information on pharmacokinetic properties (sections 4.2, 4.4 and 5.2); - update the information on pregnancy as requested in the 7th Annual Reassessment (S-036) and 9th PSUR assessment and to review the information on lactation (section 4.6); - delete pregnancy and lactation contraindications (section 4.3) further to the assessments of the 9th PSUR and FU2 029.1; - update the safety information in line with the SmPC guideline and results of a further reassessment of preclinical and clinical data, and post-marketing events (sections 4.8 and 5.3). The Package Leaflet was proposed to be updated in accordance. Additionally, the MAH also proposed wording in	15/03/2012	20/04/2012	SmPC, Annex II, Labelling and PL	For further information please refer to the scientific conclusion: H-000474-II-0038-G-AR.

	section 6.6 of the SmPC and section 3 of the PL regarding the recommendations of use and hygiene during nebulisation treatment with Ventavis which was requested as part of the outcome of the 9th PSUR. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 8.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.3.z - Implementation of change(s) requested 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 C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
S/0039	Annual re-assessment.	19/01/2012	15/03/2012		
IA/0037/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name	16/08/2011	n/a	SmPC, Labelling and PL	

	and/or address of the MAH 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.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.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				
II/0033	The MAH has updated the SmPC of Ventavis to adapt the text to the revised Company Reference Safety Information. The Package Leaflet is amended accordingly and has undergone a Consultation with Patient target groups. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/01/2011	21/02/2011	SmPC and PL	An extensive revision of the SmPC affecting sections 4.1 to 4.9, 5.1 to 5.3, 6.6 and 10 has been made. Important changes which should be highlighted were those made to: - Sections 4.2. and 4.4. relating to patients with renal impairment: change to reflect that patients with creatinine clearance of ?30ml/min should follow the same dosing recommendations as patients with hepatic impairment. - Section 4.4 relating to syncope: changes made to give more detail and alert physicians to the fact that the presence of concomitant conditions or medicines may increase the risk of syncope. - Section 4.5. relating to concomitant use of vasodilators and antihypertensive agents: wording of the section has been amended to reflect the potential increase in risk of hypotension when these medicines are administered together. - Section 4.5. relating to concomitant use of other platelet

					inhibitors: the section has been reworded to draw attention to the theoretically increased risk of bleeding. -Section 4.8. - formal revision of this section as follows: -- The frequencies of ADRs from clinical trials given in crude incidences instead of comparative incidences (iloprost vs. placebo/control). -- For the ADRs as provided in the section "post-marketing experience" the study data was reviewed to see whether a frequency could be determined. ADRs from spontaneous reporting for which no frequency could be determined following this approach, are included in the table under the category 'frequency unknown'. -- When appropriate, ADRs from clinical trials and from post marketing experience have been listed in one table. - Section 5.1. - a short description of the STEP study (C200-002) with the objective to mention the lack of new adverse effects or acute signal of any adverse effects when Ventavis is associated to bosentan. Additional text has been included but stressing that the STEP study was not designed or powered to assess long-term efficacy and tolerance of the combination.
S/0036	Annual Re-assessment	20/01/2011	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable.
II/0032	Update of section 4.8 of the SmPC regarding the following terms: "Pharyngolaryngeal pain", "throat	18/11/2010	20/12/2010	SmPC and PL	This variation is consequential to the review of a PSUR within an annual reassessment and concerns an update of

	irritation", "mouth and tongue irritation", "dysgeusia", "hypersensitivity" and "rash". The Package Leaflet has been 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				section 4.8 of the SmPC to update the following adverse reactions and their frequencies: "Pharyngolaryngeal pain", "throat irritation", "mouth and tongue irritation", "dysgeusia", "hypersensitivity" and "rash". The Package Leaflet has been updated accordingly. Further changes were made to the product information to bring it in line with QRD template version 7.3.
N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/09/2010	n/a	PL	
IA/0034/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.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	03/08/2010	n/a		
N/0031	Update of Labelling to delete text on 1ml ampoule label. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/05/2010	n/a	Labelling	
S/0030	Annual re-assessment.	21/01/2010	19/03/2010	Annex II	

IA/0029	IA_28_Change in any part of primary packaging material not in contact with finished product	17/11/2009	n/a	SmPC and PL	
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/06/2009	n/a	PL	
S/0025	Annual re-assessment.	19/03/2009	27/05/2009	PL	5th Annual re-assessment The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of Ventavis, recommended that amendment of Annex IIIB (Package Leaflet) of the Commission Decision is necessary and that the marketing authorisation remains under exceptional circumstances.
IB/0027	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	31/03/2009	n/a		
IB/0026	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	17/02/2009	n/a		
IA/0024	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	31/10/2008	31/10/2008	SmPC, Labelling and PL	
IA/0023	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	24/10/2008	24/10/2008	SmPC, Labelling and PL	
R/0018	Renewal of the marketing authorisation.	26/06/2008	02/09/2008	SmPC, Labelling and	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and

				PL	sufficiently demonstrated and therefore considers that the benefit/risk profile of Ventavis continues to be favourable. However, based upon the safety profile of the product which requires close monitoring of several adverse events, and since a specific obligation to provide long-term data on the safety and efficacy of Ventavis is not yet fulfilled, the CHMP is of the opinion that one additional five-year renewal on the basis of pharmacovigilance grounds is required. In addition, the CHMP decided that the MAH should continue to submit yearly PSURs.
II/0020	Change to SPC sections 4.2 and 5.2 following review of FUM Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	28/07/2008	SmPC and PL	Following the review of a FUM, the product information for Ventavis has been amended to include the results of a pharmacokinetic study comparing the I-Neb nebuliser to the Prodose nebuliser. Section 4.2 "Posology and method of administration" of the SPC has been updated to mention the faster delivery of the solution with I-Neb as compared to the 3 other suitable nebulisers mentioned in the SPC (i.e. Halolite, Prodose and VentaNeb). Results from the supportive pharmacokinetic study are described in section 5.2 "Pharmacokinetic properties" of the SPC. The Package Leaflet has been amended accordingly.
II/0019	Change to SPC section 4.4 and 4.8 Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	28/07/2008	SmPC and PL	Following the review of the 4th annual re-assessment of Ventavis, the CHMP requested that the product information for Ventavis (iloprost) should be amended to include a warning risk of occurrence of bronchospasm after inhalation of iloprost in section 4.4. In addition, further to the review of adverse events reported during the post-marketing period, the following adverse reactions were added to section 4.8 of the SPC: vomiting, nausea, diarrhoea, dyspnoea, bronchospasm and wheezing. The Package

					Leaflet has been amended accordingly.
IA/0021	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	12/06/2008	12/06/2008	SmPC, Labelling and PL	
II/0017	Changes to the manufacturing process for the active substance. Change(s) to the manufacturing process for the active substance	19/03/2008	31/03/2008		
S/0015	Annual re-assessment.	24/01/2008	24/01/2008		4th Annual re-assessment The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of Ventavis, recommended that no amendment of the Product Information is necessary and that the marketing authorisation remains under exceptional circumstances
IA/0016	IA_09_Deletion of manufacturing site	16/01/2008	n/a	SmPC and PL	
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/10/2007	n/a	PL	
II/0011	Update of Summary of Product Characteristics, Labelling and Package Leaflet	26/04/2007	30/05/2007	SmPC, Annex II, Labelling and PL	Further to the 3rd annual re-assessment by the CHMP, the MAH was asked to update section 4.8 of the SPC to add the adverse drug reaction 'peripheral oedema'. In addition, the MAH took the opportunity to update the annexes in line with the latest QRD templates (v. 7.2), including Braille. Furthermore, editorial changes have been introduced throughout the annexes.

					With regards to peripheral oedema, the following information has been added to section 4.8 of the SPC: "Peripheral oedema is a very common symptom of the disease itself, but can also occur under therapy. The occurrence of peripheral oedema can be related to the deterioration of the disease or insufficient effectiveness of the product." The Package Leaflet has been updated accordingly.
IA/0012	IA_01_Change in the name and/or address of the marketing authorisation holder IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	30/03/2007	n/a	SmPC, Annex II, Labelling and PL	
S/0010	Annual re-assessment.	24/01/2007	24/01/2007		Further to the CHMP review on the third annual reassessment, the product remains under exceptional circumstances.
II/0009	Change(s) to the manufacturing process for the finished product Change(s) to the manufacturing process for the finished product	21/09/2006	27/09/2006		
II/0008	Update of Summary of Product Characteristics and Package Leaflet	27/04/2006	08/06/2006	SmPC and PL	Further to the assessment of the study C200-004 ("QT study") by CHMP, the MAH was asked to update section 4.8 Undesirable effects of the SmPC in order to include

					dizziness related to hypotension, chest pain, pharyngolaryngeal pain, nausea and jaw pain. The Patient leaflet is amended accordingly.
S/0007	Annual reassessment.	01/06/2006	01/06/2006		Further to the CHMP review on the second annual reassessment, the product remains under exceptional circumstances.
II/0006	New presentation(s)	23/03/2006	02/05/2006	SmPC, Labelling and PL	
II/0005	Update of Summary of Product Characteristics and Package Leaflet	28/07/2005	05/09/2005	SmPC and PL	
S/0003	Annual re-assessment.	18/11/2004	07/03/2005	Annex II	The benefit/risk ratio remains favorable and the marketing authorisation remains under exceptional circumstances.
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/11/2004	n/a	Labelling and PL	
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/10/2004	n/a	PL	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/02/2004	13/04/2004	PL	