Volibris

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/0067	To update sections 4.8 and 5.1 of the SmPC following the assessment of Art 46 procedure (EMEA/H/C/000839) based on final results from study AMB114588; this is an open-label, long term extension study for treatment of pulmonary arterial hypertension in paediatric patients aged 8 years up	14/03/2024		SmPC, Annex II and PL	Please refer to the Scientific Summary "h-839-AR-II-67-en"

[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).

	to 18 years who have participated in AMB112529 and in whom continued treatment with ambrisentan is desired. In addition, the MAH took the opportunity to implement minor editorial changes to Annex II and to the Package Leaflet. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				
PSUSA/129/202306	Periodic Safety Update EU Single assessment - ambrisentan	08/02/2024	n/a		PRAC Recommendation - maintenance
IB/0066	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	31/03/2022	n/a		
IB/0065	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	02/12/2021	n/a		
X/0061/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency A.7 - Administrative change - Deletion of manufacturing sites	22/07/2021	22/09/2021	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion Volibris-H-C-839-X-0061-G

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0064	A.7 - Administrative change - Deletion of manufacturing sites	19/02/2021	22/09/2021	Annex II and PL	
PSUSA/129/202006	Periodic Safety Update EU Single assessment - ambrisentan	11/02/2021	n/a		PRAC Recommendation - maintenance
IAIN/0063	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	21/01/2021	n/a		
IB/0060	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	15/05/2020	n/a		
IA/0059	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	11/09/2019	n/a		
IA/0058	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	30/08/2019	n/a		
II/0055	Submission of an updated Risk Management Plan	14/02/2019	21/10/2019	Annex II	Removal of the provision of the educational materials for

	(RMP) version 8.1 in order to remove the provision of the educational materials for healthcare professionals given the availability of the SmPC and the experience of using ambrisentan and to revise the educational materials for patients as requested by the PRAC in the PSUR procedure PSUSA/00000129/201706. The Annex II of the product information is updated accordingly. In addition, the MAH also took the opportunity to update the Annex II as requested by the Portuguese Agency following the approval of the last update to the educational materials (risks of decreases in haemoglobin or haematocrit, renal impairment, peripheral oedema and fluid retention, and hypersensitivity reaction) and to correct typographical errors. The requested variation proposed amendments to the Annex II and to the Risk Management Plan (RMP). 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				healthcare professionals given the availability of the SmPC and the experience of using ambrisentan as requested by the PRAC in the PSUR procedure PSUSA/00000129/201706. Patients continue to be informed with a clear and concise message on the risk of "hepatotoxicity" and "teratogenicity" through additional risk minimisation measures, mainly with the patient reminder card. The Annex II of the product information is updated accordingly.
IAIN/0057/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.c.1 - Change to importer, batch release	31/01/2019	21/10/2019	Annex II and PL	

	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				
II/0054	Update of sections 4.2 and 5.3 of the SmPC based on results of a juvenile nonclinical toxicology study. The Risk Management Plan version 7.9 (in version 2 of the RMP template) has been updated accordingly. In addition, the Marketing authorisation holder (MAH) corrected typographical errors including the rash frequency in section 4.8 of the SmPC and the date of renewal; and introduced minor update in the braille section. Moreover, the MAH took the opportunity to combine version of the SmPCs for the different strengths. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/10/2018	21/10/2019	SmPC, Labelling and PL	In juvenile rats administered ambrisentan orally once daily during postnatal day 7 to 26, 36 or 62, a decrease in brain weight (−3% to -8%) with no morphologic or neurobehavioral changes occurred after breathing sounds, apnoea and hypoxia were observed. These effects occurred at exposures approximately 1.8 to 7 times human paediatric exposures at 10 mg (age 9 to 15 years), based on AUC. The clinical relevance of this finding to the paediatric population is not fully understood.
T/0056	Transfer of Marketing Authorisation	12/10/2018	29/10/2018	SmPC, Labelling and PL	
PSUSA/129/201706	Periodic Safety Update EU Single assessment - ambrisentan	11/01/2018	n/a		PRAC Recommendation - maintenance
IB/0053/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a	05/12/2017	n/a		

	re-test period/storage period supported by real time data B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data				
IB/0051	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	26/04/2017	19/04/2018	SmPC, Labelling and PL	
PSUSA/129/201606	Periodic Safety Update EU Single assessment - ambrisentan	12/01/2017	n/a		PRAC Recommendation - maintenance
IAIN/0050	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	12/12/2016	n/a		
IB/0049	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	03/10/2016	n/a		
II/0047/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/07/2016	n/a		

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/129/201506	Periodic Safety Update EU Single assessment - ambrisentan	14/01/2016	n/a		PRAC Recommendation - maintenance
II/0041	Extension of indication for the treatment of pulmonary arterial hypertension (PAH), in adult patients of WHO Functional Class (FC) II to III including use in combination treatment; as a consequence sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. A warning related to the increase in peripheral oedema and anemia with the combination therapy is introduced in section 4.4. Section 4.8 is updated accordingly to include updated frequencies of ADRs observed in the AMBITION study and with a new ADR introduced (sudden hearing loss) in case of use in combination therapy. The Package Leaflet is updated in accordance. In addition, the annex II is updated with a minor change in the key messages to healthcare professionals and also in line with the latest version of the QRD template. A change to the list of local representatives is also introduced in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/10/2015	20/11/2015	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion Volibris-H-C-839-II-0041

IA/0046	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	19/11/2015	n/a		
II/0039	The MAH has provided the clinical study report for the post-authorisation safety study 'AMB110094 (VOLT)', and as a consequence minor editorial changes have been implemented in secion 4.4 of the SmPC. An updated RMP version 6.4 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/11/2015	27/10/2016	SmPC, Annex II and PL	N/A
IA/0045/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	24/09/2015	n/a		
IB/0043	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	25/08/2015	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IAIN/0042/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	15/07/2015	20/11/2015	Annex II and PL	
PSUV/0040	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
II/0038	Update of SmPC section 4.8 to add the ADRs 'vision blurred' and 'visual impairment'. The Package Leaflet has been updated accordingly. In addition, the applicant took the opportunity to make editorial changes to the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	27/05/2015	SmPC and PL	As part of this application, the MAH provided a cumulative review as requested following the assessment of the last PSURs. This cumulative review included a discussion regarding spontaneous safety reports, data of clinical trials, literature review and disproportionality analysis scores using data from the FDA Spontaneous Reporting System (SRS)/Adverse Event Reporting System (AERS) database. In the light of all safety data provided, there is enough evidence to support a possible causal relationship between ambrisentan and the ADRs 'vision blurred' and 'visual impairment'. Therefore, these ADRs have been included in the SmPC and Package Leaflet for ambrisentan. The safety data provided as part of the cumulative review

					do not change the benefit/ risk balance for ambrisentan, which remains positive for the authorised indication(s).
PSUV/0037	Periodic Safety Update	10/07/2014	n/a		PRAC Recommendation - maintenance
II/0035/G	This was an application for a group of variations. Update to sections 4.5 and 5.2 of the SmPC in light of new information contained from the study "Effect of Ambrisentan on Human Hepatic Uptake and Efflux Transporters". The MAH also proposed corrections to the wording of the rat embryofoetal study results in section 5.3 of the SmPC and made an editorial change in section 4.2. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/06/2014	27/05/2015	SmPC, Annex II and PL	In this variation additional information on pharmacokinetic interactions of ambrisentan indicating that the medicine is unlikely to affect transport of other molecules into the liver was included in the product information. Moreover, further clarification was added to the section of the product information with the results from the non-clinical studies.
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/02/2014	23/04/2014	PL	
IB/0036	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	12/02/2014	n/a		
II/0033	Submission of a non-clinical final study report as part of the paediatric requirements.	23/01/2014	n/a		In the European Union, Volibris is the approved for pulmonary arterial hypertension (PAH) treatment in adults. No dose recommendations are available for children and

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				adolescents for the time being. A Paediatric Investigation Plan (PIP) was submitted and agreed with the Paediatric Committee (PDCO) (EMA Decision P/0062/2013 issued 26th March 2013). This PIP refers to the condition "Primary and secondary pulmonary hypertension" and includes the following non-clinical measures: • Two-week juvenile animal study to determine tolerability and toxicokinetics of ambrisentan. • Eight-week juvenile animal study to determine oral toxicology and toxicokinetic of ambrisentan including an 8 weeks recovery period. The objective of this variation is to submit the study report of the two-week juvenile animal study to determine the tolerability and toxicokinetics of ambrisentan. The CHMP considers that the results from the tolerability and toxicokinetics study of ambrisentan in juvenile rats do not alter the overall benefit risk assessment of Volibris for the treatment of pulmonary arterial hypertension in adults.
PSUV/0032	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
IG/0279	A.1 - Administrative change - Change in the name and/or address of the MAH	18/04/2013	23/04/2014	SmPC, Labelling and PL	
R/0030	Renewal of the marketing authorisation.	15/11/2012	14/01/2013	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 Volirbis continues to be adequately and sufficiently demonstrated and therefore considers that the benefit risk profile of Volibris continues to be favourable in the treatment of adult patients with pulmonary arterial

					hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. The CHMP is also of the opinion that the renewal can be granted with unlimited validity.
II/0026	Update of sections 4.3 and 5.1 of the SmPC after the assessment of the 7th PSUR, in order to add a contraindication in idiopathic pulmonary fibrosis (IPF) with or without secondary pulmonary hypertension, and to add information about a clinical study in patients with IPF. 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	21/06/2012	03/08/2012	SmPC	For further information please refer to the scientific conclusion: H-000474-VAR-II-0026-en.
IB/0029/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 and/or limits of an AS, starting material/intermediate/reagent - Other variation	16/07/2012	n/a		
II/0025	Update of section 4.8 of the SmPC following assessment of the 7th PSUR, to include the term "epistaxis". The Package Leaflet is updated in accordance.	19/04/2012	25/05/2012	SmPC and PL	In the assessment of the 7th PSUR (period covered: 15.12.10 - 14.06.11) the MAH was requested to include " epistaxis" as an ADR in section 4.8 of the SmPC, under the category of frequency "common", based on the frequency

	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				observed in two controlled- clinical trials.
II/0024	Update of section 4.8 of the SmPC in order to add the terms "asthenia" and "fatigue" following the evaluation of the 6th PSUR in which a cumulative review of cases of asthenia/fatigue was requested by the CHMP. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the 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	15/03/2012	13/04/2012	SmPC and PL	A cumulative review of cases of asthenia/fatigue was requested by the CHMP after the assessment of the 6th PSUR. This review was submitted by the MAH on 24 October 2011. Following this review, the MAH concluded that the data regarding time to onset and recovery after discontinuation of ambrisentan therapy in those cases of asthenia and fatigue occurring within one month of starting ambrisentan, as well as the recurrence of the asthenic condition upon restart of ambrisentan therapy in some cases support at least a reasonable possibility of a causal relationship to ambrisentan. In view of this the MAH updated section 4.8 of the SmPC to include asthenia and fatigue as undesirable effects with a frequency of "common". The package leaflet was updated accordingly.
IG/0150/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	05/04/2012	n/a		

II/0021	Update of sections 4.4, 4.6 and 5.1 of the SmPC in order to update the warning regarding reductions in haemoglobin concentrations, to include updated information regarding male fertility, and to include data from the ambrisentan ARIES-E study (A long term study of ambrisentan in pulmonary arterial hypertension subjects having completed AMB-320 OR AMB-321). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/02/2012	21/03/2012	SmPC	Ambrisentan, a selective ETA receptor antagonist, has shown to be effective in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease (PAH-CTD). In order to provide more information on the long-term effects of ambrisentan, patients in studies AMB-320 and AMB-321 had the option of continuing (or starting, if on placebo) ambrisentan treatment through a long-term extension study, AMB-320/321-E (ARIES E). The available information provided suggests a substantial improvement in survival at 1, 2 and 3 years in the PAH population compared to that which would ordinarily be anticipated. The observed probability of survival for subjects receiving Volibris (combined Volibris dose group) at 1, 2 and 3 years was 93%, 85% and 79% respectively. In addition, descriptive data on exposure and main primary endpoint in the ARIES E study (incidence and severity of adverse events) has also been included in section 5.1 of the SmPC. The distinction between IPAH and PAH-CTD is not considered necessary. Regarding safety, the ADRs identified in the ARIES-E study are consistent with the known safety profile of ambrisentan and/or the natural history and the seriousness of the disease. This study has provided evidence of long-term persistence in haemoglobin reductions, information which has been included in section 4.4 of the SmPC. This study has also provided data on 2-year risk of developing ALT/AST elevations >x3ULN, long-term persistence in BP decreases that have been included in section 4.4 of the SmPC. Lastly, although no clear evidence of a detrimental effect of ambrisentan long-term exposure on sperm count

					was found in ARIES-E study, chronic administration of ambrisentan was associated with changes in markers of spermatogenesis, and this has been reflected in section 4.6 of the SmPC.
II/0019	Update of sections 4.4 and 4.8 of the SmPC, following the assessment of the 6th PSUR, in order to include information on anaemia requiring transfusion, and to reorganize the adverse reactions and frequency categories into a single table. The Package Leaflet was updated in accordance. In addition, the MAH took the opportunity to update section 6 of the Package Leaflet in order to include the full address of the Manufacturer. 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	16/02/2012	21/03/2012	SmPC and PL	Following the assessment of 6th PSUR in May 2011, the MAH was requested to submit a type II variation to include information on the potential severity of anaemia and cases of anaemia requiring transfusion in the SmPC. A cumulative review of patients who developed anaemia that required transfusion was submitted leading to changes in section 4.4 of the SmPC. A footnote with this information was also added to the table of adverse drug reactions in section 4.8. The package leaflet was updated accordingly. In this variation the MAH also reviewed section 4.8 of the SmPC following the Guideline on SmPC (rev.2, Sep. 2009) recommendations, and merged into a single table all adverse drug reactions (from clinical studies and from spontaneous reporting) with their respective frequency categories.
IAIN/0027	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	14/03/2012	n/a		
IB/0023/G	This was an application for a group of variations. B.I.c.2.z - Change in the specification parameters and/or limits of the immediate packaging of the AS - Other variation B.I.c.1.a - Change in immediate packaging of the AS	20/01/2012	n/a		

	- Qualitative and/or quantitative composition				
II/0020	Update of section 5.3 of the SmPC in order to update the preclinical safety information further to a review of rat carcinogenicity data, together with a correction to the information on the rat embryofoetal development. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/11/2011	14/12/2011	SmPC	Carcinogenicity studies in both mice and rats were previously submitted and reviewed as part of the Marketing Authorisation Application for Volibris. In the original rat study, histological analysis revealed a number of non-neoplastic findings in the heart, spleen, kidney, nasal cavity, lung, testes and dental dysplasia of the incisors. Haematological correlates associated with the nasal cavity findings included increased red cell parameters. These changes are considered to be directly or indirectly related to the pharmacological activity of ambrisentan. The NOAEL for non-neoplastic findings was lower than the low dose of 10 mg/kg/day, corresponding to <34.8 and <24.6 µg.h/mL in males and females, respectively. The conclusion of this study was that there were no treatment-related increases in the incidence of tumours. Upon further review of the data from this rat study by the Japanese Health Authorities, a statistically significant increase in the incidence of mammary gland fibroadenoma was identified in males treated at the highest dose level (mean dietary dose of 42 mg/kg/day). As a result of this assessment, the MAH proposed new wording for Section 5.3 Preclinical safety data. The MAH also made a correction in section 5.3 of the SmPC as the statement referring to the rat embryofoetal study results was incomplete. After reviewing the data submitted the CHMP considers that the proposed amendments to the SmPC do not alter the overall favourable benefit risk assessment of ambrisentan

					for the treatment of pulmonary arterial hypertension.
II/0017	Following the CHMP assessment on cumulative overview of the hepatic safety profile (FUM 021) MAH has applied to update sections 4.4 and 4.8 of the SmPC to include information on autoimmune hepatitis and hepatic injury. The Package Leaflet has been updated accordingly. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	21/07/2011	18/08/2011	SmPC and PL	In December 2010, the MAH was requested by the CHMP to provide a review of the hepatic safety profile of ambrisentan. Following this request the MAH provided a cumulative review of relevant clinical trial data and spontaneous cases with hepatic adverse events that were assessed as FUM021. As a result of the review of the data provided it was concluded that there are no new concern but some additions in Sections 4.4 and 4.8 of the SmPC regarding autoimmune hepatitis and hepatic injury were recommended. With this type II variation MAH has applied to update sections 4.4 and 4.8 of the SmPC to include information on autoimmune hepatitis and hepatic injury. The Package Leaflet has been updated accordingly.
IB/0018	C.I.3.a - 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 - Changes with NO new additional data are submitted by the MAH	04/07/2011	n/a	SmPC	
IA/0016	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	04/05/2011	n/a	Annex II and PL	
II/0014	Upon request of the CHMP after assessment of 4th ambrisentan PSUR the MAH updated section 4.8 of the SmPC and Section 4 of the PIL to add new safety information relating to increase of hepatic transaminases. In addition, minor editorial changes have been made to SmPC and PL to adapt to QRD	20/01/2011	21/02/2011	SmPC and PL	Section 4.8 of the SmPC has been updated to add "hepatic transaminases increased" as an adverse drug reaction with a frequency of common, following the Guideline on the Summary of Product Characteristics (September 2009).

	template version 7.3. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IA/0015	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	04/02/2011	n/a		
IG/0034/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV 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.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 C.I.9.h - Changes to an existing pharmacovigilance	06/01/2011	n/a	Annex II	

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system 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				
II/0012	Update of Summary of Product Characteristics. Update of Summary of Product Characteristics	18/02/2010	23/03/2010	SmPC	Update of section 4.4 of the SPC to include a warning for Pulmonary veno occlusive disease (PVOD) to warn healthcare professionals of the risk of pulmonary oedema induced by vasodilating agents (i.e. endothelin receptor antagonists) in patients with PAH.
II/0011	Update of Summary of Product Characteristics and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	23/03/2010	SmPC and PL	Following the assessment of the 3rd PSUR, the MAH was requested to submit a type II variation to add the hypotension, syncope, nausea, vomiting, and diarrhoea to section 4.8 of the SPC as undesirable effects of unknown frequency. The Package leaflet is updated accordingly.
II/0009	Update of Summary of Product Characteristics and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	23/03/2010	SmPC and PL	Further to CHMP request based on the results of a drug-drug interaction study with rifampicin, sections 4.4 , 4.5 and 5.2 of the SPC are amended. Information of transient (approximately 2-fold) increase in ambrisentan exposure without clinically relevant effect on ambrisentan exposure is introduced in sections 4.5 interaction with other medicinal products and section 5.2 pharmacokinetic properties. In addition, a warning statement is added in section 4.4 to inform that patients on ambrisentan therapy should be closely monitored when starting treatment with rifampicin.

					The Package leaflet is updated accordingly. Other minor information concerning receptor binding is introduced in section 5.1 of the SPC . Furthermore, text and drawings are introduced in the package leaflet to provide instructions on how to open the child resistant blister packaging.
II/0010	Update of the Detailed Description of the Pharmacovigilance System (DDPS) including change of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II has been updated with the new version number. Changes to QPPV Update of DDPS (Pharmacovigilance)	17/12/2009	20/01/2010	Annex II	The DDPS has been updated (version 7.2) to reflect the change of the QPPV as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements.
II/0008	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.2, 4.5 and 5.2 of the Summary of Product Characteristics (SPC) further to the results of a drug-drug interaction study with cyclosporine A (FUM 001). The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/11/2009	21/12/2009	SmPC and PL	At the time of the granting of the initial marketing authorisation, the Marketing Authorisation Holder (MAH) made the following commitment to perform a drug-drug interaction (DDI) study with cyclosporine (FUM 001). The MAH conducted a phase 1, open-label, parallel-design, single-center study to assess the effect of multiple dose administration of CsA on the steady-state PK of ambrisentan and its circulating metabolite, 4 hydroxymethyl ambrisentan and to assess the effect of multiple dose administration of ambrisentan on the steady-state PK of CsA in healthy subjects. Steady-state co-administration of ambrisentan and cyclosporine A resulted in a 2-fold increase in ambrisentan

					exposure in healthy volunteers. This may be due to the inhibition by cyclosporine A of transporters and metabolic enzymes involved in the pharmacokinetics of ambrisentan. Therefore the dose of ambrisentan should be limited to 5 mg once daily when co-administered with cyclosporine A and the patient should be carefully monitored. Multiple doses of ambrisentan had no effect on cyclosporine A exposure, and no dose adjustment of cyclosporine A is warranted. The Product information has been updated accordingly.
II/0006	Update of Summary of Product Characteristics, Annex II and Package Leaflet Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/07/2009	28/08/2009	SmPC, Annex II and PL	Update of section 4.8 of the Summary of the Product Characteristics (SPC) to add the adverse drug reactions pruritus, dizziness, chest pain and chest discomfort, further to the request of the CHMP following the assessment of the 1st PSUR. The Package Leaflet has been updated accordingly. The MAH also proposed minor changes to Sections 2 and 5.2 of the SPC, and to update the email address of the local representative in Denmark in Section 6 of the Package Leaflet. In addition, the MAH took the opportunity to update the version number of the Risk Management Plan in Annex II with the latest agreed version 3.
IA/0007	IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	28/04/2009	n/a		
II/0005	Changes to QPPV Update of DDPS (Pharmacovigilance)	19/03/2009	07/04/2009	Annex II	Update of the Detailed Description of the Pharmacovigilance System (DDPS) and change of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II of the Product Information is

					updated with the agreed version number of the DDPS (version 6.2). In addition, the MAH took the opportunity to update Annex II with the latest agreed version number of the Risk Management plan (version 3.0).
II/0004	Update of Section 4.5 (Interaction with other medicinal products and other forms of interaction) and Section 5.2 (Pharmacokinetic properties) of the SPC based on the results of two new drug interaction studies with tadalafil and with an oral contraceptive pill, respectively. Update of Summary of Product Characteristics	22/01/2009	26/02/2009	SmPC	Two new pharmacokinetic drug interaction studies with tadalafil and with an oral contraceptive pill were submitted in this variation application. The results of the drug interaction study with tadalfil showed Co-administration of ambrisentan with tadalafil (phosphodiesterase inhibitor, substrate of CYP3A4) in healthy volunteers did not significantly affect the pharmacokinetics of either tadalafil or ambrisentan. In a clinical study in healthy volunteers, steady-state dosing with ambrisentan 10 mg once daily did not significantly affect the single-dose pharmacokinetics of the ethinyl estradiol and norethindrone components of a combined oral contraceptive. Based on this pharmacokinetic study, ambrisentan would not be expected to significantly affect exposure to oestrogen- or progestogen based contraceptives.
II/0003	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) with regards to heart failure associated with fluid retention and worsening dyspnoea of unclear aetiology further to safety review conducted by the MAH during the preparation of the 1st PSUR. The Package Leaflet is proposed to be updated accordingly. Additionally, the MAH took the opportunity to make a minor editorial change to the ATC code in section 5.1, make a minor formatting update within section 5.2 and correct the	18/12/2008	26/01/2009	SmPC, Labelling and PL	Further to post-marketing reports of heart failure (with or without evidence of fluid retention) from spontaneous and clinical study sources, the MAH conducted a safety review of these events. The MAH has selected case reports of acute right ventricular failure, cardiac failure, cardiac failure congestive, left ventricular failure, right ventricular failure, ventricular failure, pulmonary oedema, and pulmonary congestion received up to 8th April 2008. There were a total of 122 reports. Of these 122 reports, 82 had associated fluid retention events (fluid retention, general

	animal models quoted within section 5.3 of the SPC. Furthermore, the Marketing Authorisation Numbers and Date of First Authorisation have been added to the SPC and labelling where appropriate. Update of Summary of Product Characteristics, Labelling and Package Leaflet				oedema, or peripheral oedema). Based on this review, the MAH proposed to include in section 4.8 of the SPC "Cardiac failure (associated to fluid retention)" as a cardiac adverse reaction identified through post-marketing surveillance and occurring with an unknown frequency. Additionally, the warning in section 4.4 was reworded to state that fluid retention shortly after starting ambrisentan may lead to decompensated heart failure and that pre-existing fluid overload should be managed prior to starting the drug. In addition, further to post-marketing reports of dyspnoea, in particular, reports of dyspnoea occurring shortly after starting ambrisentan therapy, the MAH has performed a cumulative review of reports of dyspnoea (dyspnoea, dyspnoea exertional, respiratory distress, asthma, hypoxia, and wheezing) identified up to 15 February 2008. A total of 108 cases of dyspnoea were retrieved. In 44 there was no information to assess time to onset. Among the remaining 64 cases, 32 involved a time to onset of ? 1 week, 10 had a time to onset > 1 week and ? 3 weeks, and 22 had a time to onset > 3 weeks. Regarding the 32 cases presented within the first week, all were spontaneous reports and 17 were medically confirmed. These cases provide some evidence of a causal association with ambrisentan. Based on this review, the MAH proposed to include dyspnoea in section 4.8 of the SPC as a respiratory ADR iden
IB/0002	IB_11_c_Change in batch size of active substance or intermediate - more than 10-fold	30/05/2008	n/a		

IB/0001	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	20/05/2008	n/a		