Stayveer

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/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/10/2024		PL	
IG/1738/G	This was an application for a group of variations. B.II.a.4.a - Change in coating weight of oral dosage	16/05/2024		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).

	forms or change in weight of capsule shells - Solid oral pharmaceutical forms 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				
WS/2583	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.6 of the SmPC to update the wording concerning breast feeding based on literature and post marketing data. The Package Leaflet is updated accordingly. In addition, the MAH 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 data	08/02/2024		SmPC, Labelling and PL	Section 4.6 of the SmPC has been updated to state that data from a case report describe the presence of bosentan in human milk in a low concentration. There is insufficient information about the effects of bosentan on the breastfed infant. A risk to the breastfed infant cannot be excluded. Breast-feeding is not recommended during treatment with bosentan. For more information, please refer to the Summary of Product Characteristics.
IG/1619	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	11/07/2023	n/a		
WS/2404	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	09/02/2023	16/02/2024	SmPC, Labelling and PL	

	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product				
IG/1538	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	08/08/2022	n/a		
WS/2260	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	07/07/2022	n/a		
PSUSA/425/202111	Periodic Safety Update EU Single assessment - bosentan	10/06/2022	n/a		PRAC Recommendation - maintenance
WS/2052/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. Grouped variation application; • Type II variation C.I.4: Update of section 4.6 of the SmPC to correct the information related to male fertility based on a review of study AC-052-402 carried out by the MAH. • Type IA variation, A.7: Deletion of a batch	10/06/2021	07/06/2022	SmPC, Annex II and PL	The information regarding the clinical study of bosentan in men with PAH (AC-052-402) has been updated regarding the proportion of subjects with a decreased sperm concentration of at least 50% from baseline after 6 months of treatment. For more information, please refer to the Summary of Product Characteristics.

	release site Actelion Manufacturing GmbH, Grenzach-Wyhlen, Germany. In addition, the WSA took the opportunity to update the list of local representatives in the Package Leaflet. The WSA also took the opportunity to correct some errors in the national translations. A.7 - Administrative change - Deletion of manufacturing sites C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/425/202011	Periodic Safety Update EU Single assessment - bosentan	10/06/2021	n/a		PRAC Recommendation - maintenance
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/09/2020	07/06/2022	Labelling and PL	
PSUSA/425/201911	Periodic Safety Update EU Single assessment - bosentan	11/06/2020	n/a		PRAC Recommendation - maintenance
IAIN/0031/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.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	10/04/2020	15/09/2020	Annex II and PL	

IA/0029	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	12/12/2019	n/a		
II/0028	Update of section 4.2 of the SmPC in order to include that patients should be given the Package Leaflet and the Patient Alert Card which are included in the pack and update of annex II.D to remove the Prescriber kit from the additional risk minimisation measures and also to remove the obligation to implement a formal "Controlled Distribution System" in EU countries following the assessment of LEG 10.2. The RMP version 11 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the contact details of the local representative in the UK, to bring the PI in line with the latest QRD template version 10, and with the guideline on Excipients in the labelling and package leaflet of medicinal products for human use (EMA/CHMP/302620/2017), and to implement some corrections to the Bulgarian translations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	05/09/2019	15/09/2020	SmPC, Annex II, Labelling and PL	
II/0027	Submission of the final report from study AC-052-516 (a category 1 study). This is a non-interventional observational study of the disease characteristics and	11/07/2019	15/09/2020	Annex II	

	outcomes of Pulmonary Arterial Hypertension in children and adolescents in real-world clinical settings. Annex IID is updated accordingly. An updated RMP version 10 has was agreed during the procedure. 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				
PSUSA/425/201811	Periodic Safety Update EU Single assessment - bosentan	14/06/2019	n/a		PRAC Recommendation - maintenance
T/0025	Transfer of Marketing Authorisation	08/02/2019	11/03/2019	SmPC, Labelling and PL	
IA/0024/G	This was an application for a group of variations. 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.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)	08/08/2018	n/a		

II/0023	Update of Annex II.D and the RMP (version 9.2) following the submission of the final (13th) study report of the DUO Registry (a Category 3 non-interventional post-approval safety study and additional risk minimisation measure in the bosentan European Risk Management Plan). The MAH took the opportunity to include some editorial changes in the SmPC and to update the list of local representatives in the PL. 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	12/07/2018	11/03/2019	SmPC, Annex II and PL	
PSUSA/425/201711	Periodic Safety Update EU Single assessment - bosentan	14/06/2018	n/a		PRAC Recommendation - maintenance
R/0021	Renewal of the marketing authorisation.	09/11/2017	08/01/2018		Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Stayveer in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/425/201611	Periodic Safety Update EU Single assessment - bosentan	20/07/2017	26/09/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/425/201611.
IB/0018/G	This was an application for a group of variations. B.I.d.1.a.1 - Stability of AS - Change in the re-test	25/09/2017	n/a		

	period/storage period - Reduction B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS				
IA/0020/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	04/08/2017	n/a		
IA/0019	A.7 - Administrative change - Deletion of manufacturing sites	04/08/2017	n/a		
IB/0017	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/05/2017	26/09/2017	SmPC, Annex II, Labelling and PL	
PSUSA/425/201511	Periodic Safety Update EU Single assessment - bosentan	21/07/2016	22/09/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/425/201511.
IB/0015/G	This was an application for a group of variations. B.II.e.1.b.1 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Solid, semi-solid and non-sterile liquid pharmaceutical forms B.II.e.1.b.1 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Solid, semi-solid and non-sterile liquid	15/09/2016	26/09/2017	SmPC, Labelling and PL	

	pharmaceutical forms				
IG/0665	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	10/03/2016	n/a		
WS/0899/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. Submission of a revised RMP in order to align the additional risk minimisation measures of three safety concerns (`Pulmonary oedema associated with veno-occlusive disease', `Interaction with sildenafil' and `Interaction with antiretrovirals'), with the requirements defined in Annex II of the Marketing Authorisation. The RMP is also being updated with the outcome of previous procedures and other corrections. In addition, Annex II has been modified to reflect that the submission cycle of interim reports of the paediatric registries should be 3-yearly. Furthermore, the MAH took the opportunity to align the product information with the latest QRD template version 9.1 and to update the list of local representatives in the package leaflet. 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	25/02/2016	22/09/2016	SmPC, Annex II, Labelling and PL	

	where significant assessment is required C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUSA/425/201411	Periodic Safety Update EU Single assessment - bosentan	25/06/2015	20/08/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/425/201411.
II/0011	Update of SmPC sections 4.2, 4.5, 4.6, 4.8, 5.1, 5.2 and 5.3 to reflect non-clinical and clinical data generated in studies conducted according to the agreed Paediatric Investigation Plan for bosentan (EMEA-000425-PIP02-10-M04) in line with application II-66 for Tracleer (bosentan) approved by CHMP in November 2014. The Annex II and the Package Leaflet have been updated accordingly. Further, the MAH took the opportunity to make editorial changes in the SmPC and to update the contact details of the local representatives in the Package Leaflet. In addition, taking into account the new data in the paediatric population, an updated version of the RMP (version 7) aligned with RMP	25/06/2015	28/07/2015	SmPC, Annex II and PL	For further information, please refer to the scientific discussion 'Stayveer-H-C-2644-II-11'.

	version 7 for Tracleer was provided. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/06/2014	19/12/2014	PL	
PSUV/0006	Periodic Safety Update	12/06/2014	n/a		PRAC Recommendation - maintenance
IG/0441/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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 the finished or intermediate product - Minor change in the manufacturing process	23/05/2014	n/a		
IB/0007/G	This was an application for a group of variations. 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	10/04/2014	19/12/2014	SmPC, Labelling and PL	

	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				
II/0003	To replace sites responsible for manufacture of active substance. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	20/02/2014	n/a		
IB/0005/G	This was an application for a group of variations. C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	09/02/2014	19/12/2014	SmPC, Labelling and PL	
IAIN/0004	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	08/01/2014	19/12/2014	Annex II and PL	
IG/0352/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters	05/09/2013	n/a		

	and/or limits of the finished product - Tightening of specification limits B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				