Tracleer

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/0107	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/10/2024		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	12/01/2024	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	08/07/2022	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/0097	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/09/2020	08/07/2022	PL	
PSUSA/425/201911	Periodic Safety Update EU Single assessment - bosentan	11/06/2020	n/a		PRAC Recommendation - maintenance
IAIN/0096/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	26/02/2020	13/07/2020	Annex II and PL	

	responsible for importation and/or batch release - Not including batch control/testing				
IA/0094	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/0092	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 086.2. 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	13/07/2020	SmPC, Annex II, Labelling and PL	

IA/0093	A.7 - Administrative change - Deletion of manufacturing sites	29/07/2019	n/a		
II/0091	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 outcomes of Pulmonary Arterial Hypertension in children and adolescents in real-world clinical settings. Annex II 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	11/07/2019	13/07/2020	Annex II	
PSUSA/425/201811	Periodic Safety Update EU Single assessment - bosentan	14/06/2019	n/a		PRAC Recommendation - maintenance
N/0089	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/12/2018	13/07/2020	PL	
T/0088	Transfer of Marketing Authorisation	11/09/2018	08/11/2018	SmPC, Labelling and PL	
IA/0087/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters	07/08/2018	n/a		

	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)				
II/0086	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	08/11/2018	SmPC, Annex II and PL	
PSUSA/425/201711	Periodic Safety Update EU Single assessment - bosentan	14/06/2018	n/a		PRAC Recommendation - maintenance
IG/0839	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	20/11/2017	08/11/2018	SmPC, Annex II and PL	

	responsible for importation and/or batch release - Not including batch control/testing				
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/0081/G	This was an application for a group of variations. B.I.d.1.a.1 - Stability of AS - Change in the re-test 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	25/09/2017	n/a		
IA/0083	A.7 - Administrative change - Deletion of manufacturing sites	04/08/2017	n/a		
IA/0082	A.7 - Administrative change - Deletion of manufacturing sites	04/08/2017	n/a		
IB/0080	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/05/2017	19/07/2017	SmPC, Annex II, Labelling and PL	
IB/0077/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	19/07/2017	SmPC, Labelling and PL	

	pharmaceutical forms				
PSUSA/425/201511	Periodic Safety Update EU Single assessment - bosentan	21/07/2016	09/09/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/425/201511.
IG/0720	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	16/08/2016	19/07/2017	Annex II and PL	
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.	25/02/2016	18/08/2016	SmPC, Annex II, Labelling and PL	

	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 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				
IB/0073	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)	25/11/2015	18/08/2016	SmPC	
IG/0612	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 -	07/09/2015	18/08/2016	Annex II and PL	

	Not including batch control/testing				
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.
N/0069	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/06/2015	20/08/2015	PL	
II/0066	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). 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) was agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/11/2014	06/02/2015	SmPC and PL	For further information, please refer to the scientific discussion 'Tracleer-H-C-401-II-66'.
PSUV/0065	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	23/05/2014	n/a		

	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				
II/0062	The requested variation proposed amendments to the Summary of Product Characteristics, labelling, Annex II 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	19/09/2013	13/12/2013	SmPC, Annex II and PL	Update of the full Product Information due to extensive QRD comments included resulting in review of the previously submitted data. Clarifications are introduced in several sections of the SmPC. The Package Leaflet and Labelling were proposed to be updated accordingly. Furthermore, the MAH proposed this opportunity to bring the Annex II in line with the latest QRD template version 9. The requested variation proposed amendments to the Summary of Product Characteristics, labelling, Annex II and Package Leaflet.
IG/0352/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters 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	05/09/2013	n/a		
II/0059	Update of SmPC sections 4.2 and 5.2 SmPC for the	18/10/2012	22/11/2012	SmPC	In a pharmacokinetic crossover study (AC-052-116), 16

	32 mg strength, upon request by the CHMP following the assessment of FUM-C-061, to include information about the Pharmaokinetics of the adult and pediatric formulations based on the results of clinical study AC-052-116. Further, the MAH took the opportunity to implement editorial changes in sections 5.1 and 5.2 for 32 mg strength and 62.5 and 125 mg film coated tablets. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				healthy adult subjects received 62.5 mg bosentan using the 62.5 mg film-coated tablet formulation or 64 mg bosentan using the 32 mg dispersible tablet formulation. Following treatment with the dispersible tablet, exposure to bosentan was lower than with the film-coated tablet (ratio of geometric means for AUC0-□ 0.87 [90% CI: 0.78, 0.97]). Tmax and t1/2 of bosentan were not significantly affected by the formulation.
IAIN/0061/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	12/11/2012	13/12/2013	SmPC, Labelling and PL	
II/0056	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/09/2012	25/10/2012	SmPC and Annex II	
II/0058	Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS. To replace the manufacturer for active substance(bosentan) and the active substance milling site. B.I.a.1.z - Change in the manufacturer of AS or of a	18/10/2012	18/10/2012		

	starting material/reagent/intermediate for AS - Other variation				
IA/0060	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	27/09/2012	n/a		
IAIN/0057/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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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	23/05/2012	n/a		
R/0055	Renewal of the marketing authorisation.	16/02/2012	20/04/2012	SmPC, Annex II, Labelling and PL	
II/0054/G	This was an application for a group of variations. The MAH proposed to update Section 5.1 of the SmPC for Tracleer based on updated long-term data obtained from the final reports of 2 open-label (OL) extensions of clinical studies AC-052-364 (EARLY - OL) and AC-052-409 (BREATHE-5 - OL). C.I.4 - Variations related to significant modifications	17/11/2011	19/12/2011	SmPC	Updated long-term data were generated from 2 open label extension studies AC-052-364 (EARLY - OL) and AC-052-409 (BREATHE-5 - OL). Preliminary results were already included in the SPC in section 5.1. In this variation, updated descriptive results of the efficacy and safety results generated in the final study reports including the limitations of the data have been introduced in the section 5.1 of the SmPC.

	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				
II/0051	Update of 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	20/01/2011	28/02/2011	SmPC, Annex II, Labelling and PL	Further to CHMP request, the MAH has applied to update Section 4.8 of the SmPC and Section 4 of the Package Leaflet in accordance with the new SmPC guideline. Furthermore, other changes have been introduced upon CHMP request in section 4.4, in relation to hepatotoxicity to bring the product in line with other products of the same class. In addition, minor editorial changes related to SPC/QRD have been introduced in the product information.
IA/0053/G	This was an application for a group of variations. B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions	10/01/2011	n/a		
IA/0052/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	11/06/2010	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				
II/0049	Update of Summary of Product Characteristics and Package Leaflet	18/03/2010	22/04/2010	SmPC and PL	Update of section 4.4 further to CHMP request related to the results of study AC-052-211, an exploratory safety study conducted in patients with COPD. (FUM 56.2) Tracleer is not indicated in patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease (COPD), however a warning statement is introduced as follows: Safety and tolerability of bosentan was investigated in an exploratory, uncontrolled 12-week study in 11 patients with pulmonary hypertension secondary to severe COPD (stage III of Gold classification). An increase in minute ventilation and a decrease in oxygen saturation were observed and the most frequent adverse event was dyspnea, which resolved with discontinuation of bosentan." In addition, minor linguistic changes to the PI are introduced for 4 languages (Bulgaria, Slovenia, Hungary and Poland).
II/0047	Update of Summary of Product Characteristics and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	17/12/2009	20/01/2010	SmPC and PL	Update of section 4.8 of the SPC to add leukopenia and neutropenia reported during the post-marketing experience, further to the CHMP request of the 11th PSUR assessment. The Package Leaflet is updated accordingly. In addition, a minor change in section 4.2 is introduced following QRD review.

					The Package leaflet (sections 2 and 4) is also amended to bring the package leaflet in line with the SPC. Addition of side effects which were already mentioned in the SPC have been introduced. Furthermore, the MAH provided amendments to local representatives in the package leaflet. (GR, DK, NO, PL, IS and FI).
II/0043	Addition of an alternative site for the manufacture of the active substance. Quality changes	23/07/2009	20/08/2009		
IB/0048	IB_17_a_Change in re-test period of the active substance	05/08/2009	n/a		
II/0040	Update of sections 4.4, 4.5 and 5.1 of the SPC further to the results of a drug-drug interaction study with lopinavir/ritonavir conducted at the request of the CHMP (FUM 043). Information on interaction with other antiretroviral agents is also included. Furthermore, the list of local representatives has been updated in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	07/07/2009	SmPC and PL	At the request of the CHMP, the Marketing Authorisation Holder conducted a drug-drug interaction study between bosentan and lopinavir/ritonavir. Co-administration of Tracleer 125 mg twice daily and lopinavir+ritonavir 400+100mg twice daily during 9.5 days in healthy volunteers, resulted in initial trough plasma concentrations of bosentan that were approximately 48-fold higher than those measured after Tracleer administered alone. On day 9, plasma concentrations of bosentan were approximately 5-fold higher than with Tracleer administered alone. Inhibition by ritonavir of transport protein mediated uptake into hepatocytes and of CYP3A4, thereby reducing the clearance of bosentan, most likely

					causes this interaction. When administered concomitantly with lopinavir+ritonavir or other ritonavir-boosted protease inhibitors, the patient's tolerability of Tracleer should be closely monitored with special attention, at the beginning of the initiation phase, to the risk of hypotension and to liver function tests. An increased long-term risk of hepatic toxicity and haematological adverse events cannot be excluded when bosentan is used in combination with antiretroviral medicinal products. After co-administration of Tracleer for 9.5 days, the plasma exposures to lopinavir and ritonavir decreased to a clinically non significant extent (by approximately 14% and 17%, respectively). However, full induction by bosentan might not have been reached and further decrease of protease inhibitors cannot be excluded. Appropriate monitoring of the HIV therapy is recommended. Similar effects would be expected with other ritonavir-boosted protease inhibitors. No specific recommendation can be made with regard to co-administration with other available antiretroviral agents due to the lack of data. It is emphasized that due to a marked hepatotoxicity of nevirapine that could cumulate with bosentan liver toxicity, this combination is not recommended.
IB/0046	IB_38_c_Change in test procedure of finished product - other changes	02/07/2009	n/a		
X/0039	X-3-iv_Change or addition of a new pharmaceutical form	23/04/2009	01/07/2009	SmPC, Labelling and PL	The MAH submitted an extension application to the marketing authorisation for a new pharmaceutical form/new strength: 32 mg dispersible tablet.

					Please refer to Scientific Discussion Tracleer-H-C-401-X-39.
II/0041	Update of the Summary of Product Characteristics with regard to the posology in paediatric patients in section 4.2 of the SPC, further to the results of clinical studies and a review of the literature and post-marketing experience. Consequently, sections 4.8 and 5.2 of the SPC were updated. The Package Leaflet was updated accordingly. Annex II was updated with the revised version number of the Risk Management Plan. The Product Information was also updated in line with QRD template and changes to the SPC, Labelling and the Package Leaflet were therefore agreed. Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/04/2009	01/07/2009	SmPC, Annex II, Labelling and PL	Based on the CHMP review of data on safety and efficacy from Study BREATHE-3, FUTURE-1, a review of the literature and post-marketing experience, the CHMP considered that the information on posology in paediatric PAH patients in section 4.2 was to be updated as follows: "For paediatric patients aged 2 years or older, the optimal maintenance dose has not been defined in well-controlled studies. However, pediatric pharmacokinetic data have shown that bosentan plasma concentrations in children were on average lower than in adult patients and were not increased by increasing the dose of Tracleer above 2 mg/kg twice daily (see section 5.2). Based on these pharmacokinetic results, higher doses are unlikely to be more effective, and greater adverse event rates cannot formally be excluded in young children if the dose is increased. No clinical study has been conducted to compare the efficacy/safety ratio of 2 mg/kg to 4 mg/kg twice daily in children. There is only limited clinical experience in paediatric patients under 2 years of age." The CHMP also agreed to update sections 4.8 and 5.2 further to the results of these studies. Please also refer to the clinical aspects of the Scientific Discussion Tracleer-H-C-401-X-39.

IA/0045	IA_25_b_02_Change to comply with Ph. - compliance with EU Ph. update - excipient	22/06/2009	n/a		
IA/0042	IA_05_Change in the name and/or address of a manufacturer of the finished product	19/03/2009	n/a		
II/0037	Extension of Indication	26/06/2008	29/07/2008	SmPC, Annex II and PL	The MAH applied for an extension of indication to include in section 4.1 of the SPC that some improvements have also been shown in patients with PAH WHO functional class II. As a consequence, sections 4.4, 4.8 and 5.1 of the SPC have been updated. Annex II has been updated using standard text to reflect the latest version of the risk management plan agreed by the CHMP (version dated 23 May 2008). In addition, editorial changes were also included in the Package Leaflet and the list of local representatives has been updated. Please refer to Scientific Discussion Tracleer-H-C-401-II-37.
IA/0038	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	14/02/2008	n/a		
II/0034	Update of Summary of Product Characteristics, Labelling and Package Leaflet	18/10/2007	18/12/2007	SmPC, Annex II, Labelling and PL	Further to a request of the CHMP during the assessment of the 7th PSUR to submit an action plan to reduce the rate of pregnancy, the MAH applied for a type II Variation to amend sections 4.4 (Special warnings and special precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction) and 4.6 (Pregnancy and lactation) of the SPC. The patient reminder card and package leaflet have been updated accordingly.

					One of the main safety concerns with Tracleer is related to the potential teratogenicity that was identified during its preclinical development. Tracleer is contraindicated during pregnancy and in women of childbearing potential who are not using reliable methods of contraception. Furthermore, due to the induction potential of bosentan on CYP isoenzymes, it has been anticipated that Tracleer may render hormonal contraceptives ineffective. A total of 57 pregnancies have been reported since Tracleer was introduced on the market, including 53 following a maternal exposure (0.5% of female patients of childbearing potential exposed to bosentan). More than half of cases of maternal exposure were reported with "no information on birth control", "no birth control" or "inadequate birth control (only hormonal contraception)". Therefore, it was considered that the information to patients and prescribers about bosentan and pregnancy should be improved. In sections 4.4 and 4.5 of the SPC, the information on the use in women with childbearing potential was reinforce to highlight the risk of hormonal contraceptive failure due to the pharmacokinetic interaction with Tracleer and the need to use appropriate additional or alternative method of contraception. Section 4.6 was updated to reinforce that Tracleer is contraindicated during pregnancy and that before the initiation of Tracleer treatment in women of child-bearing potential, the absence of pregnancy should be checked, appropriate advice on reliable methods of contraception

					prov
II/0035	The MAH applied for a type II variation to update sections 4.4 and 4.8 of the SPC with the adverse events of anaemia, haemoglobin decreased and thrombocytopaenia reported during the post-marketing period further to a request from the CHMP. The package leaflet has been updated accordingly. The MAH also updated section 4.9 of the SPC following a case of overdose received during the post-marketing period. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	31/10/2007	SmPC and PL	The MAH applied for a type II variation to update sections 4.4 and 4.8 of the SPC with the adverse events of anaemia, haemoglobin decreased and thrombocytopaenia reported during the post-marketing period further to a request from the CHMP. The package leaflet has been updated accordingly. Further to the review of 157 cases of thrombocytopenia received worldwide, this undesirable effect was added to section 4.8 of the SPC with an "uncommon" frequency. Based on the review of 193 cases of anaemia requiring blood transfusion received worldwide, the warning in section 4.4 on haemoglobin concentration decrease and section 4.8 of the SPC were reinforced. Section 4.9 of the SPC was also updated with details of a case of overdose with 10,000 mg bosentan received during the post-marketing period.
IA/0036	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	02/08/2007	n/a		
R/0033	Renewal of the marketing authorisation.	22/03/2007	13/06/2007	SmPC, Annex II, Labelling and PL	
II/0029	Update of section 4.1 with subsequent changes in sections 4.2, 4.4, 4.8 and 5.1. In support of the variation to extend the indication, the applicant presents two new additional clinical	22/03/2007	07/06/2007	SmPC, Annex II and PL	Please refer to the Scientific discussion: Tracleer-H-401-II-29.

	studies in patients with systemic sclerosis and active digital ulcer disease based on results from two pivotal studies (RAPIDS-1 and RAPIDS-2). Extension of Indication				
II/0027	Update of Section 4.1 to extend the indication in PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology. Subsequent changes have been made to Sections 4.4, 4.8 and 5.1. In support of this application, the MAH presented three new additional clinical studies: in PAH associated with congenital heart disease with shunts, in PAH associated with HIV infection. Extension of Indication	21/09/2006	27/10/2006	SmPC, Annex II, Labelling and PL	Please refer to the Scientific discussion: Tracleer-H-401-II-27.
IA/0032	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	07/09/2006	n/a	Annex II and PL	
II/0028	Update of Summary of Product Characteristics and Package Leaflet	27/06/2006	10/08/2006	SmPC and PL	The MAH applied for a revised SPC 4.8 following reported cases of hepatic cirrhosis and hepatic failure in post marketing. A strengthening of section 4.4 warnings and precautions was also proposed to ensure appropriate monitoring of hepatic enzymes during the whole course of treatment. The package leaflet was revised accordingly.
IA/0030	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	07/06/2006	n/a		
IA/0031	IA_38_a_Change in test procedure of finished	06/06/2006	n/a		

	product - minor change to approved test procedure				
IB/0026	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	08/12/2005	n/a	SmPC	
II/0025	Update of Summary of Product Characteristics, Labelling and Package Leaflet	13/10/2005	15/11/2005	SmPC, Annex II, Labelling and PL	Update of information regarding drug-drug interactions with hormonal contraceptives, rifampicine and sildenafil in sections 4.5 and 4.6 of the SPC. The Package Leaflet and patient reminder card have been updated accordingly. Furthermore, a warning statement regarding co-administration with strong CYP3A4 inducers is added in section 4.4. In addition, the periodicity of PSUR submission was amended in Annex II of the Product information to be changed to a yearly cycle with additional 6 monthly liver reports
II/0024	Update of Summary of Product Characteristics and Package Leaflet	15/09/2005	19/10/2005	SmPC and PL	Update of Summary of Product Characteristics - section 4.4 special warnings and special precautions for use and update of Package Leaflet Amendment of section 4.4 following this variation procedure under special populations: Cases of pulmonary oedema have been reported with vasodilatators (mainly prostacyclin) when used in patients with pulmonary veno-occlusive disease. Consequently, should signs of pulmonary oedema occur when Tracleer is administered in patients with PAH, the possibility of associated veno-occlusive disease should be considered. In the post-marketing period there have been rare reports of pulmonary oedema in patients treated with

					Tracleer who had a suspected diagnosis of pulmonary veno-occlusive disease.
IB/0023	IB_33_Minor change in the manufacture of the finished product	22/08/2005	n/a		
IB/0021	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	22/08/2005	n/a		
II/0020	Quality changes	27/07/2005	02/08/2005		
IA/0022	IA_32_a_Change in batch size of the finished product - up to 10-fold	28/07/2005	n/a		
II/0016	Update of Summary of Product Characteristics, Labelling and Package Leaflet	21/04/2005	16/06/2005	SmPC, Labelling and PL	Section 5.1of the SPC: There are no studies to demonstrate beneficial effects on survival of treatment with Tracleer. However, long-term vital status was recorded for all 235 patients who were treated with bosentan in the two pivotal placebo-controlled trials (AC-052-351 and AC-052-352) and/or their two uncontrolled, open-label extensions. The mean duration of exposure to bosentan was 1.9 years ± 0.7 years; [min : 0.1 ; max : 3.3 years] and patients were observed for a mean of 2.0±0.6 years. The majority of patients were diagnosed as PPH (72%) and were in WHO functional class III (84%). In this total population, Kaplan-Meier estimates of survival were 93% and 84% after 1 and 2 years after the start of treatment with Tracleer, respectively. Survival estimates were lower in the subgroup of patients with PAH secondary to systemic sclerosis. The estimates may have been influenced by the initiation of epoprostenol treatment in 43/235 patients.

IA/0019	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	03/03/2005	n/a		
IA/0018	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	03/03/2005	n/a		
IA/0017	IA_05_Change in the name and/or address of a manufacturer of the finished product	17/02/2005	n/a		
S/0015	Annual re-assessment.	16/09/2004	30/11/2004	Annex II	
II/0014	Update of Summary of Product Characteristics, Labelling and Package Leaflet	29/07/2004	13/09/2004	SmPC, Labelling and PL	
II/0013	Change(s) to the manufacturing process for the active substance Quality changes	17/12/2003	23/12/2003		
I/0012	20a_Extension of shelf-life or retest period of the active substance	24/10/2003	30/10/2003		
S/0004	Annual re-assessment.	24/07/2003	24/10/2003	Annex II	
IB/0011	20_Extension of shelf-life as foreseen at time of authorisation	24/10/2003	n/a	SmPC	
I/0006	03_Change in the name and/or address of the	08/08/2003	22/09/2003	SmPC,	

	marketing authorisation holder			Labelling and PL	
I/0005	01_Change following modification(s) of the manufacturing authorisation(s)	04/07/2003	08/07/2003		
II/0002	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	26/06/2003	SmPC and PL	
I/0001	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	20/09/2002	17/10/2002	Annex II and PL	