Adcirca

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
IB/0038/G	This was an application for a group of variations. B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP -	04/07/2024		SmPC, Annex II, Labelling 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).

	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 B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
PSUSA/2841/ 202210	Periodic Safety Update EU Single assessment - tadalafil	22/06/2023	01/09/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2841/202210.
IG/1620	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	01/08/2023	n/a		
X/0035/G	This was an application for a group of variations. Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one Annex I_2.(c) Change or addition of a new strength/potency	15/12/2022	24/02/2023	SmPC, Labelling and PL	Please refer to Scientific Discussion: Adcirca-H-C-1021-X-0035-G-AR.

N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/09/2021	19/05/2022	Labelling and PL	
WS/1940	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/01/2021	19/05/2022	SmPC, Annex II, Labelling and PL	
PSUSA/2841/ 201910	Periodic Safety Update EU Single assessment - tadalafil	11/06/2020	n/a		PRAC Recommendation - maintenance
IG/1133	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	14/08/2019	n/a		
IG/0914	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	15/03/2018	n/a		
PSUSA/2841/ 201610	Periodic Safety Update EU Single assessment - tadalafil	09/06/2017	n/a		PRAC Recommendation - maintenance
WS/1066	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2 and 5.1 of the Adcirca SmPC and update of section 5.1 of the Cialis SmPC in order	23/03/2017	19/02/2018	SmPC	Please refer to the published assessment report EMEA/H/C/WS/1066: EPAR - Assessment Report – Variation

	to reflect the results of study H6D-MC-LVJJ, a randomized, double-blind, placebo-controlled phase 3 trial of tadalafil in the treatment of Duchenne Muscular Dystrophy (DMD), to fulfil Adcirca P46 019.1 and Cialis P46 045.1. In addition the MAH took the opportunity to update section 6.6 of the SmPC to remove the statement 'no special requirements' for Adcirca and Cialis and to add the standard statement about disposal of any unused or waste material for Cialis, and to align annex II.C with the latest QRD template version 10. 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				
WS/1100	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/02/2017	19/02/2018	SmPC and PL	
WS/0993	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 4.4 of the SmPC in order to add a new warning on the risk of acute non-arteritic anterior ischemic optic neuropathy (NAION) based on	23/02/2017	19/02/2018	SmPC, Annex II, Labelling and PL	

	the results of observational study NCT00759174 and MAH conducted observational study H6D-MC-LVHQ (NCT0113110, a category 3 study in the RMP), looking at an association between the intermittent use of phosphodiesterase (PDE) type 5 inhibitors and the risk of acute NAION. The RMP (version 8.1) is updated accordingly. In addition the Worksharing applicant (WSA) took the opportunity to align the Package Leaflet with the SmPC of Adcirca and Cialis regarding the adverse drug reaction (ADR) 'priapism' and of Cialis only for the ADR 'prolonged erection', to make corrections in the German annexes and to align the product information with the latest QRD template version 10. The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP on variation to the terms of the marketing authorisation. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/0749/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation	02/12/2016	n/a		
PSUSA/2841/ 201510	Periodic Safety Update EU Single assessment - tadalafil	26/05/2016	26/05/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/2841/201510.
IG/0664	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	25/02/2016	n/a		
IG/0662	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2016	27/02/2017	SmPC, Labelling and PL	
PSUSA/2841/ 201410	Periodic Safety Update EU Single assessment - tadalafil	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/2841/201410.
WS/0762	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/07/2015	n/a		
PSUV/0019	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
PSUV/0017	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/02/2014	20/08/2015	PL	
IG/0383	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	06/12/2013	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
R/0015	Renewal of the marketing authorisation.	21/03/2013	22/05/2013	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 benifit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of Adcirca continues to be adequately and sufficiently demonstrated and therefore considers that the benefit risk profile continues to be favourable in the treatment of pulmonary arterial hypertension (PAH) classified as World Health Organisation (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.
WS/0339	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 4.8 of the SmPC of Adcirca and Cialis to add tinnitus to section 4.8 at a frequency of uncommon.The package leaflets have been updated accordingly with the SmPC change. 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	17/01/2013	12/02/2013	SmPC and PL	Update of section 4.8 of the SmPC of Adcirca and Cialis to add tinnitus to section 4.8 at a frequency of uncommon. This variation was requested by the CHMP following the review of the tadalafil PSUR 16 and is being implemented as requested by the CHMP with no new additional data being submitted. The package leaflet has been updated accordingly with the SmPC change.
WS/0321	This was an application for a variation following a	13/12/2012	24/01/2013	SmPC, Annex	The European Medicines Agency identified a signal for

	worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in order to add the terms haematuria, haematospermia and penile haemorrhage at a frequency of uncommon for both Cialis and Adcirca. The Package Leaflet is updated accordingly. This variation was requested by the CHMP following a class review of cumulative data on urogential bleeding in relation to PDE-5 inhibitors. The MAH also took the opportunity to correct a typographical error in Annex II of the product information of Adcirca. Furthermore, the PI for both products is being brought in line with the latest QRD template version 8.2. 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			II and PL	penile haemorrhage and haematospermia following the use of sildenafil when monitoring the EudraVigilance database. After an initial discussion of this signal, the Pharmacovigilance Working Party (PhVWP) requested all MAHs of PDE-5 inhibitors to submit a cumulative overview of the adverse event (AE) terms penile haemorrhage, haematospermia, haematuria and penile hematoma and a discussion on background incidence, and possible mechanisms, including a possible effect on platelet function, time relations, long term outcome, overdose, the potential for confounding, and the possibility of a pharmacological class effect. After having assessed this cumulative review the CHMP concluded that genitourinary bleeding events should be considered a class effect shared by all PDE-5 inhibitors. In response to the request from the CHMP the MAH submitted this type II variation to include haematuria, haematospermia and penile haemorrhage in section 4.8 of the SmPC with a frequency of uncommon for both Adcirca and Cialis. The package leaflet was updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 8.2.
IG/0238	B.III.2.a.1 - Change of specification('s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS	15/11/2012	n/a		
II/0011/G	This was an application for a group of variations. Update of section 4.8 of the SmPC after assessment of PSUR 15 to include the term "angioedema" with a	19/07/2012	23/08/2012	SmPC and PL	Following the review of tadalafil PSUR 15, the CHMP required the MAH to include angioedema as a listed adverse drug reaction (ADR) in the section 4.8 with a frequency of "unknown". The MAH acknowledged this

	frequency of "unknown", and update of section 4.8 to include the term "syncope" with a frequency of "common" to allign with the Company Core Datasheet (CCDS). The Package Leaflet is updated accordingly. A minor editorial change has also been made to the PL to align with the QRD template. 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 C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				request and has updated the SmPC accordingly. Following a review of the Company Core Data Sheet (CCDS) which was also submitted with PSUR 15, it was identified that the ADR "syncope", present in the CCDS as a result of post-marketing data from Cialis, had inadvertently not been included in the Adcirca SmPC. To align the SmPC with the CCDS, the MAH added "syncope" to the tabulated summary of ADRs in section 4.8 as part of this variation. This ADR was included in the SmPC with a frequency of "common" to reflect the results of the single pivotal placebo-controlled trial (H6D-MC-LVGY).
IA/0010	A.7 - Administrative change - Deletion of manufacturing sites	16/12/2011	n/a		
IA/0008/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	04/02/2011	n/a	Annex II	

IG/0031	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	17/12/2010	n/a		
II/0006	The variation concerns an update of Section 4.4 and Section 4.5 of the SPC following a request by the CHMP following the assessment of the tadalafil PSUR 11. The MAH took the opportunity to bring the current PI in line with the new SPC guideline and QRD template. 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	23/09/2010	03/11/2010	SmPC and PL	Following the assessment of PSUR 11 for tadalafil, the CHMP requested the MAH to submit a Type II variation to update Section 4.4 "Special warnings and precautions for use" regarding the efficacy and safety of Adcirca with other PDE5 inhibitors. In addition the CHMP requested that the corresponding text in Section 4.5 "Interaction with other medicinal products and other forms of interaction" is removed. The Adcirca SPC in this variation was also updated to be in line with the new guideline (effective on the 1st May 2010) and QRD template version 7.3. Part of this SPC update includes revising the tabulated summary of adverse reactions present in Section 4.8 "Undesirable effects" in order to assign a frequency to the adverse reaction classified as "Not Known". As a consequence of the update to the SPC, appropriate revisions have been proposed to the Adcirca package leaflet.
IB/0007/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	29/10/2010	n/a		

	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size				
II/0005	Update to section 4.8 of the Summary of Product Characteristics regarding cerebrovascular haemorrhagic events. In addition, the Marketing Authorisation Holder took the opportunity to update the contact details of the local representatives for Denmark, Latvia and Spain in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	21/01/2010	26/03/2010	SmPC and PL	Following the assessment of PSUR 10 for tadalafil (covering the period from 16 October 2007 - 15 October 2008) and the MAH's responses to tadalafil PSUR 10, the MAH was requested by the CHMP to update section 4.8 of the SPC by adding "(including haemorrhagic events)" after the word "stroke". The MAH has hereby submitted a type II variation to update section 4.8 of the SPC accordingly. No new data was submitted by the MAH as part of this type II variation. The CHMP considered this type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and the Package Leaflet .
II/0001	Change of Indication C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/10/2009	30/11/2009	SmPC, Labelling and PL	This type II variation concerns the change of the indication of Adcirca from erectile dysfunction to the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease. The pack sizes have been consequently changed from 2, 4, 8 and 12 tablets to 28 and 56 tablets. As a consequence,

					changes were made to sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2 and 6.5 of the Summary of Product Characteristics (SPC), Annex IIIA and the Package Leaflet. In addition, the conditions or restrictions regarding supply and use imposed on the marketing authorisation holder in Annex II have been changed to "Medicinal product subject to restricted medical prescription". A statement to that effect has also been added to section 4.2 of the SPC. Furthermore, Annex II has been updated to include the agreed version 1.3 of the Risk Management Plan. Please refer to Scientific Discussion: Adcirca-H-1021-II-01-AR.
IB/0004	IA_35_a_Change in weight of coating/capsule shells - immediate release pharm. forms IB_34_b_01_Change in colour/flavour - Increase or addition: colouring system	21/10/2009	n/a	SmPC and PL	
IB/0003	IB_02_Change in the name of the medicinal product IA_39_Change/addition of imprints, bossing or other markings	21/10/2009	n/a	SmPC, Annex II, Labelling and PL	
II/0002	To remove the specification for water in Tadalafil Lilly 20 mg tablets. Update of or change(s) to the pharmaceutical documentation	23/07/2009	30/07/2009		