Cialis

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
PSUSA/2841/ 202210	Periodic Safety Update EU Single assessment - tadalafil	22/06/2023	25/08/2023	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	01/08/2023	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	product formulation - Change that does not affect the product information				
N/0095	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/09/2021	04/02/2022	PL	
N/0094	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/03/2021	04/02/2022	Labelling	
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	04/02/2022	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 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	23/03/2017	30/01/2018	SmPC	Please refer to the published assessment report EMEA/H/C/WS/1066: EPAR - Assessment Report – Variation
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	30/01/2018	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 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	23/02/2017	30/01/2018	SmPC, Annex II, Labelling and PL	
IG/0749/G	This was an application for a group of variations.	02/12/2016	n/a		

	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				
PSUSA/2841/201510	Periodic Safety Update EU Single assessment - tadalafil	26/05/2016	22/07/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2841/201510.
IB/0084	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	03/05/2016	22/07/2016	SmPC	
IB/0080/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.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	15/03/2016	22/07/2016	SmPC and Labelling	
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	22/07/2016	SmPC, Labelling and	

				PL	
IA/0079	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 originally approved batch size	04/09/2015	n/a		
PSUSA/2841/201410	Periodic Safety Update EU Single assessment - tadalafil	25/06/2015	14/08/2015	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/0076	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
PSUV/0074	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
N/0075	Inclusion of an additional local representative of the MAH for the new Member State Croatia. The MAH also took the opportunity to make minor corrections to the Romanian Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/02/2014	14/03/2014	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				
IG/0321	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/07/2013	n/a		
IB/0071	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	26/03/2013	14/03/2014	SmPC, Labelling and PL	
IA/0070	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	05/02/2013	n/a		
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	13/02/2013	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 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	13/12/2012	21/01/2013	SmPC, Annex II and PL	The European Medicines Agency identified a signal for 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/0060	Addition of a new indication "Treatment of the signs	20/09/2012	24/10/2012	SmPC,	Please refer to scientific discussion for Cialis

	and symptoms of benign prostatic hyperplasia in adult males including those with erectile dysfunction" for the 5 mg formulation. Sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and the package leaflet have been updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			Labelling and PL	EMEA/H/C/000436 for further information.
II/0066	Update of section 4.8 of the SmPC in order to update the safety information of the tabulated summary of adverse reactions by adding angioedema and dyspnoea and to update the frequency of the adverse reaction gastro-oesophageal reflux (GERD). The Package Leaflet is 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	19/07/2012	10/09/2012	SmPC and PL	Type II variation to update Section 4.8 "Undesirable effects" of the Cialis Summary of Product Characteristics (SmPC) with the addition of the adverse drug reactions (ADR) angioedema as rare and dyspnoea as uncommon (between 0.1% and <1%) and to update the frequency of the ADR, gastro-oesophageal reflux (GERD) from uncommon to common (between 1% and 10%). This variation was requested by the CHMP following the assessment of PSUR 15.
R/0065	Renewal of the marketing authorisation.	19/07/2012	10/09/2012	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Cialis continues to be favorable. The CHMP was of the opinion that the renewal could be granted with unlimited validity.

					However the MAH will continue to submit yearly PSURs, unless otherwise specified by the CHMP.
IB/0064	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	09/03/2012	n/a		
IA/0063	A.7 - Administrative change - Deletion of manufacturing sites	16/12/2011	n/a		
N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/10/2011	n/a	PL	Update of the German local representative's contact details in the package leaflet.
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/05/2011	n/a	PL	Update of the local representatives contact details for Germany, Estonia and France. The MAH also took the opportunity to amend the European Medicines Agency's website address in the package leaflet.
IA/0058/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	22/02/2011	n/a		
II/0055	Amendment of SmPC sections 4.2 and 5.1 regarding the use of a tadalafil once-a-day regimen in men	20/01/2011	21/02/2011	SmPC and Annex II	The results from a randomized, double-blind, placebo controlled study of tadalafil in men with ED who were naïve

	with ED without the proviso that the patient first demonstrates response with an on-demand PDE5 inhibitor. Version number of the DDPS is deleted from Annex II.B. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				to treatment with a PDE5 inhibitor (study LVHX) demonstrated statistically significant improvements in all three co-primary efficacy endpoints (p<0.001). The LS mean change from baseline in the Erectile Function Domain questions of the International Index of Erectile Function was 7.3 points for tadalafil vs 3.4 points for placebo; the LS mean change from baseline in Question 2 of the subject Sexual Encounter Profile diary (ability to insert penis into vagina) was 23.8% for tadalafil vs 12.2% for placebo; and the LS mean change from baseline in Question 3 of the subject Sexual Encounter Profile diary (successful intercourse) was 39.5% for tadalafil vs 21.5% for placebo. In spite of being modest, also the effect of tadalafil on responder rate can be regarded as consistently demonstrated and clinically relevant for the intended population. No new safety concerns have been identified in this study, the most common observed adverse events being the same as those identified previously.
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		
IA/0057	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	01/12/2010	n/a		
IB/0056/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	29/10/2010	n/a		

	proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.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/0054	Following CHMP conclusions on the assessment of PSUR 11, the section 4.4 of the SmPC with regard to the concomitant use with other PDE5 inhibitors has been amended. Following conclusions from the assessment of RMP version 4, the section 4.8 of the SmPC with regard to frequencies of adverse drug reactions and section 4 of the PL were amended accordingly. The fifth level of the ATC code has been added in section 5.1 Pharmacodynamic properties. Furthermore, the SmPC is updated in line with the revised SmPC Guideline (sections 4.1, 4.2, 4.5, 4.6, 4.8, 5.1). Revisions to the list of local representatives in the PL were also made.	22/07/2010	06/09/2010	SmPC and PL	During the reporting periods for PSUR 11 there was a spontaneous report of deafness (PT) in a patient who was taking tadalafil concomitantly with another PDE5 inhibitor, sildenafil. Sudden hearing loss has been identified as an event of potential risk in association with all PDE5 inhibitors, despite the absence of a postulated probable mechanism for a role of PDE5 inhibitors in the occurrence of this event. Hence, "PDE5 Inhibitors" has been added to the statement that discusses concomitant use of tadalafil with other treatments for erectile dysfunction in the section 4.4 of the SmPC. The frequencies of adverse drug reactions (ADRs) in Section 4.8 have been updated based on an analysis of the results of 36 placebo-controlled clinical trials on erectile dysfunction in the currently approved indication and dosage. This update also addresses that during the reporting of RMP version 4 a higher incidence of sudden

	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				hearing loss among TDF treated patients compared to placebo was reported, hence the adverse events incidence rates in section 4.8 of the SmPC was updated.
IA/0053	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	14/04/2010	14/04/2010	SmPC, Labelling and PL	
II/0052	Update of Summary of Product Characteristics and Package Leaflet	21/01/2010	09/02/2010	SmPC and PL	
IB/0051	IB_17_a_Change in re-test period of the active substance	02/10/2009	n/a		
IB/0050	IB_33_Minor change in the manufacture of the finished product	18/06/2009	n/a		
IB/0049	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	18/06/2009	n/a		
IB/0048	IA_13_a_Change in test proc. for active substance - minor change IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	21/11/2008	n/a		
IA/0047	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	19/09/2008	n/a		

II/0046	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.4 and 4.5 of the SPC based on the results of four clinical pharmacology studies which evaluated the interaction between tadalafil and various alpha adrenergic receptor blocking agents. Update of Summary of Product Characteristics	24/07/2008	03/09/2008	SmPC	The CHMP reviewed four additional pharmacodynamic studies which evaluated the interaction between tadalafil (TDF) and three -adrenergic antagonists (doxazosin, tamsulosin and alfuzosin): Two studies evaluated the effects on blood pressure of doxazosin in combination with tadalafil. One study evaluated the interaction between three different dosing regimens of a single dose of 20 mg TDF and doxasozin 4 mg or 8 mg daily. Another study included TDF 5 mg and concomitant increasing doses of doxazosin up to 4 mg daily. A third study evaluated the effects on blood pressure with the coadministration of alfuzosin 10 mg and a single dose of tadalafil 20 mg. Finally, another study evaluated the effects on blood pressure of a single dose of tamusolin 0.4 mg in combination with tadalafil 5 mg daily. These studies showed that in patients who are taking alpha blockers, concomitant administration of tadalafil may lead to symptomatic hypotension in some patients. When taldalafil is co-administered with doxazosin, hypotension lasts at least twelve hours, may be symptomatic, including syncope. Therefore this combination is not recommended. Hypotension was not reported with alfuzosin or tamsulosin, although, caution should be exercised when using tadalafil

					in patients treated with any alpha-blockers, and notably in the elderly. Consequently, the SPC was updated to reflect this information.
IB/0045	IB_17_b_Change in the storage conditions for the active substance	09/04/2008	n/a		
II/0039	Update to section 4.8 of of Summary of Product Characteristics to include sudden deafness. The package leaflet is amended accordingly and the list of local representatives has also been updated. Update of Summary of Product Characteristics and Package Leaflet	21/02/2008	17/03/2008	SmPC and PL	Further to case reports of sudden deafness/hearing loss associated with the product class, the CHMP requested a cumulative review of such cases for all PDE5 inhibitors. After review of the post-marketing and clinical trial data provided, the CHMP recommended that the term "sudden deafness" be included in section 4.8 of the SPC for all PDE5 inhibitors including Cialis (tadalafil).
IA/0044	IA_09_Deletion of manufacturing site	07/03/2008	n/a		
IA/0043	IA_09_Deletion of manufacturing site	07/03/2008	n/a		
IA/0042	IA_09_Deletion of manufacturing site	07/03/2008	n/a		
IA/0041	IA_09_Deletion of manufacturing site	07/03/2008	n/a	Annex II and PL	
II/0038	Update of section 4.8 of the Summary Product Characteristics (SPC) to include 'seizures' and 'transient amnesia' following the CHMP conclusions on seventh and eighth Periodic Safety Update Reports (PSURs). Additional changes in this section were also made to be in accordance with the SPC	24/01/2008	29/02/2008	SmPC and PL	Following assessment of seventh and eighth PSURs, twenty-two cases of convulsions were identified (19 spontaneous reports and 3 from open label studies). Eight of these patients had a history of epilepsy and two others had a second fit following discontinuation of tadalafil. In 8 of the 12 remaining cases, convulsions appeared within the

	guideline. Section 4 of the Package Leaflet (PL) was amended accordingly. Furthermore changes were made following latest QRD templates. Update of Summary of Product Characteristics and Package Leaflet				first 24 hours after the last tadalafil dose (for two patients this information is unknown and the other two experienced seizures the second day after the last tadalafil dose), strongly suggesting a causal relationship. Additionally, twenty-four post-marketing reports of amnesia were identified. Some of these patients had other risk factors. However, the CHMP considered that temporal sequence in the other patients strongly suggested a causal relationship. Overall, the CHMP considered that these data supported the inclusion of 'seizures' and transient amnesia' in section 4.8 of the SPC. The Package Leaflet was amended accordingly.
T/0037	Transfer of Marketing Authorisation	17/09/2007	18/10/2007	SmPC, Labelling and PL	
R/0032	Renewal of the marketing authorisation.	19/07/2007	17/09/2007	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Cialis remains positive, but considers that its safety profile is to be closely monitored due to the limited use of the new treatment scheme of Cialis 2.5 and 5 mg to be taken once daily. Based upon the safety profile of Cialis, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
II/0031	Update of sections 4.4 and 5.1 of the Summary Product Characteristics (SPC) further to the results of study H6D-MC-LVFY, a randomised, double blind, placebo controlled, parallel study assessing the efficacy and safety of tadalafil in subjects with	21/06/2007	10/08/2007	SmPC	The CHMP reviewed the clinical study H6D-MC-LVFY and considered that although there was a lack of long term efficacy and safety data, the results were of clinical relevance in males with erectile dysfunction caused by spinal cord injury. The CHMP concluded that the overall

	erectile dysfunction (ED) caused by spinal cord injury (SCI). Update of Summary of Product Characteristics				safety and efficacy profile of Cialis was consistent with the one observed in the general ED population. Consequently, the following changes were made to the SPC: - deletion of the warning for patients with spinal cord injuries in section 4.4 - and inclusion of the main efficacy results in section 5.1
IA/0036	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	09/08/2007	n/a	Annex II, Labelling and PL	
IA/0035	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	07/08/2007	n/a		
IA/0034	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	07/08/2007	n/a		
X/0027	Annex I_2.(c) Change or addition of a new strength/potency	26/04/2007	20/06/2007	SmPC, Labelling and PL	
X/0026	Annex I_2.(c) Change or addition of a new strength/potency	26/04/2007	20/06/2007	SmPC, Labelling and PL	
IB/0033	IB_30_b_Change in supplier of packaging components - replacement/addition	15/06/2007	n/a	SmPC	
N/0029	The Marketing Authorisation Holder (MAH) applied for the inclusion of the local representatives for Romania and Bulgaria in section 6 of the Package Leaflet (PL). Additionally the MAH took the opportunity to	01/02/2007	n/a	Labelling and PL	

	introduce Braille to the outer carton. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
IA/0030	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	22/01/2007	n/a		
IA/0028	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	13/11/2006	n/a	Annex II and PL	
II/0025	This variation relates to an update of section 4.8 (Undesirable effects) of the Summary of Product Characteristics (SPC) to include information regarding epistaxis following the CHMP assessment of PSUR5 and PSUR6 covering the period 16th October 2004 - 15th October 2005. In addition following evaluation of PSUR6 the MAH proposed an additional adverse drug reaction (migraine) to be included in section 4.8 of the SPC. The corresponding sections in the Package Leaflet (PL) are updated. In addition, the MAH also took the opportunity to update the PL with post-marketing ADRs in line with section 4.8 of the SPC. Update of Summary of Product Characteristics and Package Leaflet	28/06/2006	28/07/2006	SmPC and PL	Several cases cases of epistaxis have been received post marketing. Although some of these patients had other risk factors, the close temporal relationship and the reoccurrence of epistaxis strongly suggest a causal relationship. The MAH was requested to submit a type II variation to include epistaxis in the SPC section 4.8 of tadalafil (TDF).The Marketing Authorisation Holder (MAH) also took the opportunity to review all cases of migraine reported in association with TDF use in PSURs 5/6. There were several cases reported by health care professionals plus cases from consumers. Two cases were reported as migraine without aura, one case as migraine with aura, and the remaining were reported as migraine. Two of the cases were considered serious. In some of the cases the diagnosis of migraine was supported by additional reported events (aphasia, nausea and vomiting, visual disturbance, ocular headache, dysesthesia, paresthesia). Section 4.8 was therefore updated following CHMP evaluation.
II/0024	The variation relates to an update of section 4.2 (Posology and method of administration), 4.4	28/06/2006	28/07/2006	SmPC, Annex II, Labelling	Three studies were conducted in men to assess the potential effect on spermatogenesis of CIALIS 10mg (one

	(Special warnings and special precautions for use) and 5.1 (Pharmacodynamic properties) of the SPC (Summary of Product Characteristics) to include additional information relating to semen characteristics following daily administration of tadalafil based on results of a post-marketing commitment study. Relevant sections of the Package Leaflet have been updated accordingly. In addition the MAH applied to update the product information in line with the current QRD templates. Update of Summary of Product Characteristics, Labelling and Package Leaflet			and PL	6-month study) and 20mg (one 6-month and one 9-month study) administered daily. In two of these studies a decrease in sperm count and concentration related to tadalafil treatment of doubtful clinical relevance was observed. These effects were not associated with changes in other parameters such as motility, morphology and FSH. In the study of 10 mg CIALIS for 6 months and the study of 20 mg CIALIS for 9 months, results showed a decrease in mean sperm concentrations relative to placebo. This effect was not seen in the study where the higher dose of 20 mg. CIALIS was taken daily for 6 months. In the 9-month study, decreases in sperm concentration were associated with higher ejaculatory frequency. Ejaculation frequency was not assessed in the 6-month studies. In addition there was no adverse effect on mean concentrations of reproductive hormones, testosterone, luteinizing hormone or follicle stimulating hormone with either 10 or 20 mg of CIALIS compared to placebo.
II/0022	This variation relates to an update of the Summary of Product Characteristics (SPC) section 4.3 (Contraindications) to include a statement that PDE5 inhibitors are contraindicated in patients with a previous episode of Non-arteritic anterior ischemic optic neuropathy (NAION). Sections 4.4 and 4.8 of the Summary of Product Characteristics are also amended in order to include information with regard to non-arteritic anterior ischemic optic neuropathy (NAION). Relevant sections of the Package Leaflet are updated	27/04/2006	12/06/2006	SmPC and PL	In the context of the ongoing evaluation of the NAION issue (see II-20) and considering the data available and new cases arising, it cannot be ruled out that there might be a causal relationship between PDE5 inhibitors and NAION. The CHMP agreed with the proposal to contraindicate the use of PDE5 inhibitors in patients with a previous episode of NAION as a class labelling and to continue investigating this issue. Therefore, section 4.3 of the SPC has been updated to contraindicate CIALIS in patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic

	accordingly. In addition, the MAH took the opportunity to update the contact information of the Danish, Irish and Spanish local representatives. Update of Summary of Product Characteristics and Package Leaflet				neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4). Section 4.4 of the SPC was also updated to include the following information: Visual defects and cases of non-arteritic ischaemic optic neuropathy (NAION) have been reported in connection with the intake of CIALIS and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking CIALIS and consult a physician immediately (see section 4.3). NAION is included in section 4.8 of the SPC.
IB/0023	IB_10_Minor change in the manufacturing process of the active substance	07/04/2006	n/a		
II/0020	This variation relates to an update of the Summary of Product Characteristics (SPC) section 4.4 (Special warnings and special precautions for use) to include a warning stating that PDE5 are not recommended in patients with a previous episode of Non-arteritic anterior ischemic optic neuropathy (NAION). Section 4.8 (Undesirable effects) was also amended to add Non-arteritic anterior ischemic optic neuropathy (NAION) and visual field defect and retinal vascular occlusion at the request of the CHMP. The Package Leaflet (PL) has been amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	13/10/2005	15/11/2005	SmPC and PL	Anterior ischemic optic neuropathy (AION) is an ischemic disease. It is a vascular event that is presumed to occur due to a decrease in blood flow to the small penetrating arteries that supply the optic nerve as it enters the eyeball or globe. In NAION vascular disease and arteriolosclerosis are assumed to cause infarction of the short posterior ciliary arteries supplying the anterior optic nerve. NAION is the most common acute optic nerve disease in adults over age 50. Reported incidence rates range from 2.5/100,000/year in adults over 50 from two counties in the U.S. (Johnson et al., 1994) to a rate adjusted for age and sex distribution of 10.2/100,000 (95% CI: 6.5-15.6) from the Ohmstead County study (Hattenhauer, 1997). Although the aetiology of NAION is unknown, many of its risk factors are similar to those for erectile dysfunction such as ischemic heart disease, hypertension,

					hypercholesterolemia, diabetes, and increased age (Hayreh, 1995). NAION has been an issue of concern with PDE5 inhibitors. However, the fact that some of the risk factors for NAION are likely to be present in the population exposed to these drugs have made difficult to draw any firm conclusion about the association. Pomeranz et al (2005) describe seven patients, aged between 50 and 69 years, who had typical features of NAION within 36 hours after ingestion of PDE5 inhibitors. Other articles describe cases of NAION after use of PDE5 inhibitors. Articles by Pomeranz et al (2002), Egan et al (2000), Boshier et al (2002), Cunningham et al (2001) and Gruhn et al (2005) describe additional 9 cases. However, these cases do not clarify whether the association is causally related. There is an additional publication by Dheer et al (2002). The CHMP conducted a review of cases of NAION for all authorisied PDE5 inhibitors.Although the reporting rate of NAION for the PDE5 inhibitors is below the background incidence of NAION in the general population older than 50 years of age, the temporal s
IB/0021	IB_18_Replacement of an excipient with a comparable excipient	22/08/2005	n/a	SmPC and PL	
IB/0019	IB_18_Replacement of an excipient with a comparable excipient	31/05/2005	n/a	SmPC and PL	

IB/0017	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	05/04/2005	n/a	SmPC	
II/0016	This variation relates to an update of section 4.8 (Undesirable effects) of the Summary of Product Characteristics to include information regarding cardiovascular disorders (myocardial infarction, chest pain, palpitations, tachycardia, and cerebrovascular accidents), hypotension, loss of consciousness, and syncope following the CHMP assessment of PSUR2 and PSUR3. The CHMP also requested that the paragraph on serious cardiovascular events, currently in section 4.4, be included to section 4.8 of the SPC. In addition following evaluation of PSUR4 the MAH proposes additional adverse drug reactions (hypersensitivity reactions including rash, urticaria, facial oedema, Stevens-Johnson syndrome, exfoliative dermatitis, sweating, and abdominal pain, and gastro-oesophageal reflux) to be included in SmPC section 4.8 of the SPC. The list of local representatives has been updated for Portugal and Slovenia. Update of Summary of Product Characteristics and Package Leaflet	17/02/2005	29/03/2005	SmPC and PL	Following the review of tadalafil third PSUR, the CHMP requested the MAH to include new information regarding cardiovascular disorders (myocardial infarction, chest pain, palpitations, tachycardia, and cerebrovascular accidents), hypotension, loss of consciousness, and syncope in section 4.8 of the SPC. The MAH proposed additional adverse drug reactions (hypersensitivity reactions including rash, urticaria, facial oedema, Stevens-Johnson syndrome, exfoliative dermatitis, sweating, and abdominal pain, and gastro-oesophageal reflux) to be included in SPC section 4.8. This proposal is the result of a planned analysis of cumulative tadalafil safety data included in the fourth PSUR.
IA/0015	IA_01_Change in the name and/or address of the marketing authorisation holder	01/10/2004	n/a	SmPC, Labelling and PL	

IB/0013	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	15/07/2004	15/07/2004	SmPC, Labelling and PL	
IA/0014	IA_13_a_Change in test proc. for active substance - minor change	12/07/2004	n/a		
II/0009	Update of Summary of Product Characteristics and Package Leaflet	26/02/2004	06/07/2004	SmPC and PL	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) with regards to priapism and prolonged erection, as requested by CHMP, following the review of the first Periodic Safety Update Report. The warning regarding priapism was reworded to state that agents for the treatment of erectile dysfunction, including CIALIS, should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia). Information that in postmarketing surveillance prolonged erection and priapism have been reported very rarely was also added to section 4.8 of the SPC. Corresponding changes have been included in section 4 of the Package Leaflet.
IA/0012	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	01/04/2004	n/a		
IA/0011	IA_09_Deletion of manufacturing site	01/04/2004	n/a		
IB/0010	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	30/03/2004	n/a	SmPC	

II/0006	an update of the Summary of Product Characteristics (SPC) to reflect the data from new studies. Update of Summary of Product Characteristics and Package Leaflet	25/09/2003	27/01/2004	SmPC and PL	The MAH had completed new studies in patients with erectile dysfunction. On the basis of efficacy data from these new studies and previously submitted studies, the information on the duration of action of CIALIS has been updated. In view of the data presented the CHMP concluded that efficacy of CIALIS seems to be maintained until 36 hours, the efficacy being very similar between 24 and 36 hours. However, the CHMP noted that there are no clinical data that allow the establishment of the exact duration of action for CIALIS. Therefore, in order to clearly state the maximum allowed frequency (which is considered necessary for an on demand drug which may prove inefficacious in individual patients) and to discourage too frequent unnecessary use the information on the duration of action in section 4.2 of the SPC was amended to: Continuous daily use of the medication is strongly discouraged because the long term safety after prolonged daily dosing has not been established and also because the effect of tadalafil usually lasts for longer than one day. Furthermore, the information on the clinical trials in section 5.1 was amended to reflect the new data. Corresponding changes have been included in section 3 of the Package Leaflet.
II/0005	an update in the Summary of Product Characteristics (SPC) based on duration of efficacy data from previously submitted studies and from recently completed studies. Update of Summary of Product Characteristics and	22/10/2003	27/01/2004	SmPC and PL	The MAH had completed new studies in patients with erectile dysfunction. On the basis of efficacy data from these new studies and previously submitted studies, the information on the duration of action of CIALIS has been updated. In view of the data presented the CHMP concluded that efficacy of CIALIS seems to be maintained

	Package Leaflet				until 36 hours, the efficacy being very similar between 24 and 36 hours. However, the CHMP noted that there are no clinical data that allow the establishment of the exact duration of action for CIALIS. Therefore, in order to clearly state the maximum allowed frequency (which is considered necessary for an on demand drug which may prove inefficacious in individual patients) and to discourage too frequent unnecessary use the information on the duration of action in section 4.2 of the SPC was amended to: Continuous daily use of the medication is strongly discouraged because the long term safety after prolonged daily dosing has not been established and also because the effect of tadalafil usually lasts for longer than one day. Furthermore, the information on the clinical trials in section 5.1 was amended to reflect the new data. Corresponding changes have been included in section 3 of the Package Leaflet.
IA/0008	IA_32_a_Change in batch size of the finished product - up to 10-fold	19/11/2003	n/a		
II/0004	This variation relates to an update of sections 4.3, 4.4, 4.5 and 5.1 of the Summary of Product Characteristics to reflect data from new interaction studies. Corresponding changes have been introduced in sections 2 and 3 of the Package Leaflet (PL). In addition, the Spanish telephone number and the Swedish contact details have been amended in the list of Local Representatives in the PL. Update of Summary of Product Characteristics and Package Leaflet	26/06/2003	20/10/2003	SmPC and PL	The MAH submitted results from new interaction studies. CYP450 2C19 was added to the list of CYP450 isoforms that tadalafil does not ingibit or induce in section 4.5 of the SPC based on an in vitro study and the projected in vivo inhibition. In subjects receiving concomitant tadalafil (20 mg) and doxazosin (8 mg daily), an alpha (1)-adrenergic receptor blocker, there was an augmentation of the blood-pressure-lowering effect of doxazosin. This effect was still present at 12 hours postdose and had generally disappeared at 24

					hours. The number of subjects with potentially clinically significant standing-blood-pressure decreases was greater for the combination. Some subjects experienced dizziness but no cases of syncope were reported. The combination of tadalafil and alpha blockers is therefore not recommended. Information on the interaction between tadalafil and alpha blockers has been added to section 4.4, 4.5 and 5.1. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased tadalafil (10-mg dose) exposure (AUC) 2-fold and Cmax by 15%, relative to the AUC and Cmax values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20-mg dose) exposure (AUC) 4-fold and Cmax by 22%. Ritonavir, a protease inhibitor (200 mg dose given twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20-mg dose) exposure (AUC) 2-fold with no change in Cmax. This information was added to section 4.5 of the SPC and a warning was added to section 4.4 recommending caution to be exercised when prescribing Cialis to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole and erythromicin). Section 4.5 had been updated to include information on coadministration of tadalafil 20 mg and warfarin and of tadalafil 20 mg and aspirin. Based on the results of a clinical study in which 150 subjects receiving daily doses of tadalafil 20 mg for 7 days and 0.4 mg sublingual nitroglycerin at

I/0007	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	22/07/2003	28/07/2003		
I/0001	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	19/12/2002	09/01/2003		
I/0002	15_Minor changes in manufacture of the medicinal product 15a_Change in IPCs applied during the manufacture of the product	19/12/2002	n/a		
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/12/2002	27/01/2003	PL	