Levitra

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/3098/ 202403	Periodic Safety Update EU Single assessment - vardenafil	14/11/2024	13/01/2025	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3098/202403.
N/0068	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/11/2023	13/01/2025	PL	
N/0067	Minor change in labelling or package leaflet not	20/10/2021	13/01/2025	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).

	connected with the SPC (Art. 61.3 Notification)				
WS/1750	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 5.2 (Pharmacokinetic properties) of the vardenafil SmPCs and relevant sections of the PLs to expand the information regarding vardenafil interactions with P-glycoprotein (P-gp) as a result of a general review of vardenafil pharmacokinetic properties. Editorial changes proposed by the MAH during the procedure have been accepted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/03/2020	22/03/2021	SmPC, Annex II, Labelling and PL	A general review of vardenafil pharmacokinetic properties and available literature regarding vardenafil interactions with P-glycoprotein (P-gp) and cytochrome P450 (CYP) has led to an update of the product information. In vitro data suggests a potential effect of vardenafil on P-glycoprotein substrates more sensitive than digoxin as for example dabigatran etexilate and this has been reflected in Section 5.2. of the SmPC.
PSUSA/3098/201903	Periodic Safety Update EU Single assessment - vardenafil	17/10/2019	09/12/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3098/201903.
WS/1536	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final clinical study report of study 12912 a non-interventional PASS (category 3 study) to investigate the NAION (Non-arteritic anterior ischemic optic neuropathy) risk associated with PDE5 inhibitors together with a consequential update of	16/05/2019	n/a		Early termination of NAION study 12912 had been agreed within Workshare procedure (EMEA/H/C/xxxx/WS/1390 on 6 September 2018. Based on the review of the Clinical study Report provided, the small sample size (only 10 patients) makes any statistical analysis difficult and the study is unlikely to provide value for further risk assessment of NAION associated with the class of PDE5 inhibitors indicated for the treatment of erectile dysfunction.

	the RMP. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				Considering that after termination of the NAION study only routine pharmacovigilance activities and risk minimisation measures are currently in place and vardenafil has been marketed for more than 15 years risks were considered fully characterised and appropriately managed through routine risk minimizations. Furthermore it was considered unlikely that any pharmacovigilance activity could further characterize the potential risks. Accordingly all the important potential and identified risks were removed from the RMP safety specification.
WS/1390	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 to reflect data from two post-marketing observational studies indicating an increased risk of Non-arteritic Anterior Ischaemic Optic Neuropathy (NAION) when using phosphodiesterase 5 (PDE5) inhibitors. The MAH is also terminating the Bayer NAION study 12912 and the RMP is updated accordingly to version 5.0. In addition, the PI is brought in line with version 10.0 of the QRD template and the contact details of the Bulgarian local representative are updated in the Package Leaflets. The PI for the 10 mg orodispersible tablet is updated for aspartame and sorbitol, according to the annex to the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. Some editorial amendments are also made to the PI.	06/09/2018	26/08/2019	SmPC, Labelling and PL	The analyses of the observational data suggest an approximate 2- fold increase in the risk of Non-arteritic Anterior Ischaemic Optic Neuropathy (NAION) when phosphodiesterase 5 (PDE5) inhibitor use (such as vardenafil, tadalafil and sildenafil), as a class, occurred immediately before NAION onset (within 5 half-lives), compared to PDE5 inhibitor use in a prior time period. Due to the nature of the performed observational studies, no causality between PDE5i use and NAION can be established. Nevertheless, the study results enhance the current understanding of the association and are considered clinically relevant. The RMP version 5 reflects the termination of NAION study on March 2018 as it was concluded that the study is unlikely to provide value for further risk assessment of NAION associated with the class of PDE5 inhibitors indicated for the treatment of erectile dysfunction.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/04/2018	26/08/2019	PL	
N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/12/2017	26/08/2019	PL	
IG/0852	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	08/11/2017	n/a		
T/0059	Transfer of Marketing Authorisation	15/03/2017	29/03/2017	SmPC, Labelling and PL	
IG/0774/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	16/02/2017	29/03/2017	Annex II and PL	
IG/0772/G	This was an application for a group of variations.	31/01/2017	n/a		

	B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material				
IG/0753/G	This was an application for a group of variations. B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method	16/12/2016	n/a		

	B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
PSUSA/3098/201603	Periodic Safety Update EU Single assessment - vardenafil	27/10/2016	n/a		PRAC Recommendation - maintenance
WS/0973	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	13/10/2016	n/a		
IA/0055/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites	24/08/2016	29/03/2017	SmPC, Labelling and PL	

	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)				
WS/0861	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	17/12/2015	22/01/2016	SmPC, Annex II and PL	
IB/0051	Update of the PI to QRD template vs.9 and update of the French local representative contact details in the Package Leaflet. In addition, the MAH took the opportunity to make minor editorial corrections throughout the PI. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/04/2014	09/04/2015	SmPC, Annex II, Labelling and PL	
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/01/2014	09/04/2015	PL	
IG/0391	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	11/12/2013	n/a		

IA/0048	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	10/06/2013	n/a		
IAIN/0047	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/01/2013	n/a		
WS/0313	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 update the safety information adding Penile haemorrhage, Haematospermia, and Haematuria with an uncommon frequency, further to the revision of a cumulative review, as requested by the CHMP. The Package Leaflet (PL) is updated accordingly. In addition, the MAH took the opportunity to bring in line the PL with the current SmPC and to correct some minor editorial errors. In addition, the MAH took the opportunity to delete the e-mail of local representative of Estonia in the Package Leaflet. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8.2. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	13/12/2012	21/01/2013	SmPC, Annex II and PL	The variation relates to the CHMP request to update the safety information of the product on urogenital bleeding Adverse Drug Reactions related to PDE5 inhibitor class of active substances, to which vardenafil belongs to. Following the assessment of the cumulative overview concerning the role of PDE5 inhibitors for urogenital bleeding events, it has been concluded that there is sufficient evidence for a possible relationship between PDE5 inhibitor class and penile haemorrhage, haematospermia and haematuria. As a result of this assessment the MAH for Levitra/Vivanza has been asked the introduction of Penile haemorrhage, Haematospermia, and Haematuria to Section 4.8 of the SmPC.

IG/0221	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	10/10/2012	n/a		
IAIN/0044/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 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	14/05/2012	n/a		
II/0043	The variation relates to an update of section 4.2. (Posology and method of administration) of the SmPC (Summary of Product Characteristics), and section 3. (How to take Levitra) of the Package Leaflet of Levitra 10mg orodispersible tablets to “to be taken as needed approximately 25 to 60 minutes before sexual activity”, to harmonize this information with Levitra film-coated tablets. In addition, minor changes have been made in accordance with the QRD template and for consistency throughout the	16/02/2012	19/03/2012	SmPC, Annex II, Labelling and PL	The posology between the two pharmaceutical forms was harmonised in view of the time of onset of clinical effect. This was based on previous pivotal, placebo controlled, randomized Phase III trials (Studies 12093 and 12094) conducted with Levitra 10 mg ODT as well as four placebo-controlled Phase III studies to support the Levitra 5mg, 10mg and 20 mg FCT formulation. In addition the MAH summarized previous results from clinical studies and further analyses of patients’ data from the ODT Phase III clinical program which provided pharmacokinetic results to

	product information. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				support similar time of onset of action for both ODT and FCT formulations.
WS/0207	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The variation relates to an update of section 4.4 (Special warnings and special precautions for use) and 4.5 (Interaction with other medicinal products and other forms of interaction) of the SPC (Summary of Product Characteristics) to include additional information relating to the interaction of vardenafil with alfuzosin. In addition, minor changes have been made in accordance with the QRD template and for consistency throughout the product information. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/01/2012	21/02/2012	SmPC, Annex II, Labelling and PL	Based on one interaction study conducted with vardenafil in patients with benign prostatic hyperplasia (BPH) on stable alpha-blockers alfuzosin therapy, the sections 4.4 and 4.5 of the SmPC are updated to reflect the interaction of vardenafil with alfuzosin. When vardenafil was given at doses of 5 or 10 mg on a background of stable therapy with alfuzosin, there was no symptomatic reduction in blood pressure and no hypotension was observed.
IA/0036/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH 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	19/08/2011	n/a	SmPC, Annex II, Labelling and PL	

	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release 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				
N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/05/2011	n/a	PL	Change in the German local representative's contact details in the Package Leaflet.
IB/0034	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	26/05/2011	n/a		
WS/0107	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 and the corresponding section 4 of the PL for the film-coated tablets (FCT) according the safety information for the recently approved pharmaceutical form orodispersible tablets (ODT). Additionally, the SmPC, the Labelling and the PL for the film-coated tablets have been editorially aligned with the orodispersible formulation and the list of local representatives in the PL has been updated. Finally, editorial changes have been applied to Annex II and the latest QRD template has been implemented. This was an application for a group of variations following a worksharing procedure according to	17/03/2011	20/04/2011	SmPC, Annex II, Labelling and PL	Since the safety profile of both the film-coated tablet (FCT) and the orodispersible tablet (ODT) formulations was similar, an integrated analysis of adverse drug reactions combining the orodispersible tablet studies with the film-coated tablet erectile dysfunction studies was performed. Overall, the safety data from integrated analysis of 59 clinical trials involving 17748 patients was used to support an update of the vardenafil product information. The information about undesirable effects has been updated accordingly.

	Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IB/0033/G	This was an application for a group of variations. B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes 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 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	18/04/2011	18/04/2011	SmPC, Labelling and PL	
IG/0049/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	02/03/2011	n/a		

WS/0108	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of the re-test period for the premix used in the manufacture of film-coated tablets. B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	17/02/2011	17/02/2011		
WS/0089	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of the re-test period for the active substance (vardenafil hydrochloride trihydrate). B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	17/02/2011	17/02/2011		
IB/0031	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)	19/01/2011	n/a	SmPC	
IA/0032/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance	10/01/2011	n/a	Annex II	

	system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database 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				
IB/0030/G	This was an application for a group of variations. 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 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 B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g.	03/12/2010	03/12/2010	SmPC, Labelling and PL	

	tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes 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 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				
IA/0029	B.II.a.3.a.1 - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Addition , deletion or replacement	26/10/2010	n/a		
X/0028	Annex I_2.(d) Change or addition of a new pharmaceutical form	24/06/2010	01/09/2010	SmPC, Labelling and PL	
T/0026	Transfer of Marketing Authorisation	05/06/2009	22/06/2009	SmPC, Annex II, Labelling and PL	
IA/0027	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	02/06/2009	n/a	Annex II and PL	
II/0025	Update of Summary of Product Characteristics	22/01/2009	25/02/2009	SmPC	
II/0024	Update of Summary of Product Characteristics.	26/06/2008	28/07/2008	SmPC	In a separate post marketing study of 44 healthy volunteers, single doses of 10 mg Vardenafil or 50 mg

	The variation refers to an update of sections 4.4 and 5.1 of the Summary of Product Characteristics to include information on the possible effects of vardenafil on QT interval in monotherapy and in combination with other drugs which are known to prolong QT interval. Update of Summary of Product Characteristics				sildenafil were co-administered concomitantly with 400mg gatifloxacin, a drug with comparable QT effect. Both Vardenafil and sildenafil showed an increase of Frederica QTc effect of 4 msec (vardenafil) and 5 msec (sildenafil) when compared to either drug alone. The actual clinical impact of these QT changes is unknown. The SPC sections 4.4 and 5.1 have been updated to reflect this information.
II/0023	Update of Summary of Product Characteristics and Package Leaflet. This variation refers to an update of sections 4.2, 4.4 and 4.5 of the Summary of Product Characteristics to include information on an interaction between vardenafil and clarithromycin. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	28/07/2008	SmPC and PL	Co-administration of erythromycin (500 mg three times a day), a CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 4 fold increase in vardenafil AUC and a 3 fold increase in Cmax. Although a specific interaction study has not been conducted, the in vivo studies already submitted for erythromycin are supportive of the in vivo extrapolation for clarithromycin, considering the similar inhibitory potency view in other in vivo studies, the co-administration of clarithromycin can be expected to result in similar effects on vardenafil AUC and Cmax. When used in combination with a moderate CYP 3A4 inhibitor such as erythromycin or clarithromycin, vardenafil dose adjustment might be necessary. The SPC section 4.2, 4.4 and 4.5, and the PL have been updated to reflect this information.
II/0022	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	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

	Package Leaflet				inhibitors including Levitra (vardenafil).
R/0021	Renewal of the marketing authorisation.	13/12/2007	07/02/2008	SmPC and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Levitra continues to be favourable.
II/0020	Addition of the ADRs "transient global amnesia" and "seizure" with the frequency rare to section 4.8 of the SPC according to the CHMP conclusion on the assessment of the PSURs 7 and 8 (covering the period 4 March 2006 to 3 March 2007). Update of Summary of Product Characteristics, Labelling and Package Leaflet	18/10/2007	21/11/2007	SmPC, Annex II, Labelling and PL	Update of section 4.8 of the SPC to add "transient global amnesia" and "seizures" following the CHMP conclusion on the PSURs 7 and 8. Two cases of "transient global amnesia" in patients taking part in clinical trials were identified. Five cases of "seizure" were also identified in clinical trials data. The frequency of both adverse events was characterised as rare. The Package Leaflet is amended accordingly. Changes to the product information due to the QRD version 7.2 have been made as well as to the contact details of Romanian and Bulgarian representatives.
II/0019	Quality changes	24/05/2007	29/05/2007		
II/0018	The Marketing authorisation holder (MAH) applied for a variation to update section 4.5 (Interaction with other medicinal products and other forms of interaction) of the Summary of Product Characteristics (SPC) to include information on the potential for interaction with Nicorandil. Update of Summary of Product Characteristics	18/10/2006	24/11/2006	SmPC	Section 4.5 of the Summary of Product Characteristics (SPC) was updated to include the additional information relating to the interaction of vardenafil with nitrates (see scientific discussion for procedure II/0006). Nicorandil is a compound with a nitrate component which has the potential to interact with vardenafil and therefore the MAH applied to include this additional information in the section 4.5 of the SPC. The SPC is updated as follows:

					Section 4.5 "Interaction with other medicinal products and other forms of interaction" Nicorandil is a hybrid of potassium channel opener and nitrate. Due to the nitrate component it has the potential to have serious interaction with vardenafil.
II/0017	The variation relates to an update of section 4.4 (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 the use of vardenafil in Spinal cord injury patients. Update of Summary of Product Characteristics	28/06/2006	28/07/2006	SmPC	Levitra contains vardenafil a phosphodiesterase type 5 (PDE5) inhibitor which is indicated for treatment of men with erectile dysfunction (ED). Levitra was granted a Marketing autorisation where, according to the preliminary data, the use of vardenafil in patients with ED secondary to Spinal cord injury has not been studied. Two Studies 10473 and 100608 specifically designed to provide data concerning the efficacy and safety of vardenafil in this patient population have now been conducted in this group of ED patients. Study 10473 was the larger and more encompassing of the two studies and is considered the pivotal trial. Study 100608 was conducted in Japan and utilized an open-label design. In the clinical trials vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo. The severity and level of the cord injury did not affect the efficacy results. Vardenafil was well tolerated in the

					population in Studies 10473 and 100608.
II/0016	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 accordingly. In addition, the contact details of the Icelandic local representative have been updated. Update of Summary of Product Characteristics and Package Leaflet	27/04/2006	12/06/2006	SmPC and PL	In the context of the ongoing evaluation of the NAION issue (see II-12) 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 LEVITRA in patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic 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 LEVITRA and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking LEVITRA and consult a physician immediately (see section 4.3). NAION is included in section 4.8 of the SPC. The Package Leaflet was updated accordingly.
II/0015	The variation relates to an update of section 4.4 (Special warnings and special precautions for use) and 4.5 (Interaction with other medicinal products and other forms of interaction) of the SPC (Summary	23/03/2006	05/05/2006	SmPC	Based on interaction studies conducted with vardenafil in patients with benign prostatic hyperplasia (BPH) on stable tamsulosin or terazosin therapy, plus the analysis of pooled adverse event data from 40 Phase II to IV clinical studies

	of Product Characteristics) to include additional information relating to the interaction of vardenafil with alpha-blockers. Update of Summary of Product Characteristics				conducted between January 2000 and April 2005, two post-authorisation safety studies and the review of spontaneous reports of adverse events collected through the PSURs, the sections 4.4 and 4.5 of the SPC are updated to reflect the interaction of vardenafil with alpha-blockers. When vardenafil was given at doses of 5, 10 or 20 mg on a background of stable therapy with tamsulosin, there was no symptomatic reduction in blood pressure, although 3/21 tamsulosin-treated subjects exhibited transient standing systolic blood pressures of less than 85 mmHg. When vardenafil 5 mg was given simultaneously with terazosin 5 or 10 mg, one of 21 patients experienced symptomatic postural hypotension. Hypotension was not observed when vardenafil 5 mg and terazosin administration was separated by 6 hours. Therefore, concomitant treatment should be initiated only if the patient is stable on his alpha blocker therapy. In those patients who are stable on alpha-blocker therapy, vardenafil should be initiated at the lowest recommended starting dose of 5mg. Vardenafil may be administered at any time with tamsulosin. With other alpha blockers a time separation of dosing should be considered when vardenafil is prescribed concomitantly.
II/0014	Update of or change(s) to the pharmaceutical documentation	27/04/2006	03/05/2006		
II/0013	Change(s) to the test method(s) and/or specifications for the active substance	23/03/2006	29/03/2006		
II/0012	This variation relates to an update of the Summary of Product Characteristics (SPC) section 4.4 (Special	13/10/2005	15/11/2005	SmPC, Labelling and	Anterior ischemic optic neuropathy (AION) is an ischemic disease. It is a vascular event that is presumed to occur

	warnings and special precautions for use) to include a warning stating that PDE5 inhibitors 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. In addition the labelling for the different presentations has been combined. Update of Summary of Product Characteristics, Labelling and Package Leaflet			PL	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 authorised 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
II/0010	This variation relates to an update of section 4.8 of the Summary of Product Characteristic (SPC) as requested by the CHMP following assessment of the 3rd PSUR, namely to further include information on myocardial infarction as an adverse reaction (ADR) reported post-marketing in temporal association with vardenafil. Unstable angina was also added to section 4.8 as an ADR reported in this class. In addition minor linguistic errors were corrected in the Slovakian texts. Update of Summary of Product Characteristics	23/06/2005	16/08/2005	SmPC	Based on the assessment of the Third Periodic Safety Update Report (PSUR) section 4.8 of the SPC was updated to state that in post-marketing myocardial infarction (MI) was reported in temporal association with vardenafil. Most of the patients reported had pre-existing cardiovascular risk factors. However, it is not possible to determine whether MI is related to vardenafil, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these factors.In addition, unstable angina was also added to section 4.8 of the SPC as an ADR reported in post-marketing with another medicinal product in this class.
IA/0011	IA_05_Change in the name and/or address of a manufacturer of the finished product	09/06/2005	n/a	Annex II and PL	
N/0008	The MAH applied for the addition of a security feature on the blister for Levitra. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/04/2005	n/a	Labelling	
IA/0009	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	30/03/2005	n/a		

II/0007	The variation relates to an update of section 4.8 (Undesirable Effects) of the Summary of Product Characteristics to reflect the recoding of the Adverse Drug Reactions from COSTART to MedDRA terminology and include additional adverse drug reactions. The corresponding section 4 of the Package Leaflet was revised accordingly. In addition minor linguistic changes and change of the details of the Estonian, French, Greek and Latvian Local representatives have been made in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	17/02/2005	29/03/2005	SmPC and PL	Section 4.8 (Undesirable Effects) of the Summary of Product Characteristics was updated to reflect the recoding of the Adverse Drug Reactions from COSTART to MedDRA terminology and includes additional adverse drug reactions.
II/0005	Update of Summary of Product Characteristics	26/02/2004	01/06/2004	SmPC	Based on the data provided during the initial Marketing Authorisation Application, a dose recommendation in the SPC regarding the use of vardenafil in patients with mild to moderate hepatic impairment was given following the increments in AUC and Cmax observed in those patients and taking into consideration that no adverse events neither transaminases increases were observed in those patients. Although no safety concerns have arisen during the post-marketing experience, the MAH proposed to restrict the dosing of vardenafil in these patients to a maximum of 10 mg as a precautionary measure and to allow worldwide harmonisation of the hepatic impairment dosing recommendations for vardenafil.

II/0004	Update of Summary of Product Characteristics and Package Leaflet	26/02/2004	01/06/2004	SmPC and PL	Following the availability of further post marketing and clinical trials data (reference is made to the first PSUR) the following adverse drug reactions (ADRs) were included in section 4.8 of the SPC: back pain, increased creatine kinase, myalgia, postural hypotension and watery eyes. The sentence in section 4.8 of the SPC regarding myocardial infarction was updated to read: myocardial infarction (MI) have been reported in temporal association with the use of Vardenafil and sexual activity, but it is not possible to determine whether MI is related directly to Vardenafil, or to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these factors: Corresponding changes have been included in section 4 of the PL.
II/0006	Update of Summary of Product Characteristics	21/01/2004	02/03/2004	SmPC	In order to further clarify the interactions information that is currently included in the SPC further studies were performed: nitrate study and 3 alpha-blocker studies. The nitrate study showed that symptomatic effect (hypotension or/and dizziness) was seen more frequently in the vardenafil group rather than in the placebo group following the NTG administration. The contraindication for the concomitant use of vardenafil and nitrates is therefore maintained and further information was added in section 4.5 of the SPC with regards to this interaction. The results of the alpha blocker studies demonstrated that when 5 mg vardenafil was given on a background of stable tamsulosin therapy there were no clear differences in blood pressure effects between vardenafil and placebo. When 5 mg vardenafil was given simultaneously with terazosin therapy some patients experienced hypotension. This did not occur

					when there was a six hour dosing separation between vardenafil and terazosin. Information on this findings was added to section 4.4 and 4.5 of the SPC.
II/0003	Update of Summary of Product Characteristics and Package Leaflet	21/01/2004	02/03/2004	SmPC and PL	The effect of vardenafil (10 mg and 80 mg), on the corrected QT interval was evaluated in a single dose, randomized, crossover, double-blind, placebo-controlled study in 59 healthy adult men. Single oral doses of 10mg and 80 mg of vardenafil were shown to prolong the QTc interval by a mean of 8 msec and 10 msec, respectively. The clinical relevance of this finding is unknown and cannot be generalised to all patients under all circumstances, as it will depend on the individual risk factors and susceptibilities that may be present at any time in any given patient. Sections 4.4 and 5.1 of the Summary of Product Characteristics (SPC) were therefore updated in order to include this information and to include the advice that patients with left ventricular outflow obstruction can be sensitive to the action of vasodilators. Corresponding changes have been included in the Package Leaflet.
II/0002	Update of Summary of Product Characteristics and Package Leaflet	21/01/2004	02/03/2004	SmPC and PL	Update of sections 4.3, 4.4 and 4.5 of the Summary of Product Characteristics (SPC) to reflect data from new pharmacokinetic studies concerning the interaction of vardenafil with ritonavir. The SPC included a formal warning for avoiding the concomitant use of vardenafil with potent CYP3A4 inhibitors (and a formal contraindication for men older than 75 years) based on the data coming from the interaction studies presented during the initial Marketing Authorisation application. The data submitted for this variation are consistent with the previous ones and show a clinically relevant increase in the exposure to vardenafil when coadministered with a potent CYP3A4

					inhibitor (ritonavir). A contraindication was therefore added regarding concomitant use of vardenafil with HIV protease inhibitors such as ritonavir and indinavir, as they are very potent inhibitors of CYP3A4. Information on the interaction was also added to section 4.4 and 4.5 of the SPC and reflected in the Package Leaflet.
II/0001	Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	27/01/2004	SmPC and PL	Update of section 4.8 of the Summary of Product Characteristics to reflect additional data from clinical trials. The following adverse reactions were added: abnormal liver function tests GGTP increased, somnolence, angina pectoris, myocardial ischemia, dyspnea, epistaxis, face oedema, anaphylactic reaction (including laryngeal oedema), glaucoma, priapism (Including prolonged or painful erections), conjunctivitis, rash, abnormal vision (predominantly visual disturbances, but also increased perception to light. In addition the following information was added in section 4.8:"Single cases of myocardial infarction (MI) have been reported in temporal association with the use of Vardenafil and sexual activity, but it is not possible to determine whether MI is related directly to Vardenafil, or to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these factors." These changes were also reflected in section 4 of the Package Leaflet.