Viagra

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
IAIN/0124	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	21/05/2024		SmPC and PL	

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

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X/0115	Annex I_2.(d) Change or addition of a new pharmaceutical form	14/12/2023	09/02/2024	SmPC, Annex II, Labelling and PL	
IG/1692/G	This was an application for a group of variations. B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition) B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	12/01/2024		Annex II and PL	
WS/2475/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.b.2.e - Change in test procedure for AS or	11/01/2024	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IA/0122	A.7 - Administrative change - Deletion of manufacturing sites	04/01/2024	n/a		
IG/1672/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	05/10/2023	n/a		
N/0119	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/09/2023	09/02/2024	PL	
WS/2516	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	31/08/2023	n/a		

	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
N/0117	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/03/2023	15/09/2023	PL	
IG/1545/G	This was an application for a group of variations. B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	27/09/2022	n/a		
PSUSA/2699/ 202112	Periodic Safety Update EU Single assessment - sildenafil (indicated for erectile dysfunction)	01/09/2022	n/a		PRAC Recommendation - maintenance
IB/0114	C.I.3.a - 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 - Implementation of wording agreed by the competent authority	29/08/2022	15/09/2023	SmPC and PL	To update section 4.5 of the SmPC to add a warning about the increase in hypotension observed with concomitant use of sildenafil and sacubitril/valsartan. The PL has been updated accordingly.
N/0113	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/07/2022	15/09/2023	PL	
N/0111	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/03/2022	15/09/2023	PL	

N/0110	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/12/2021	15/09/2023	PL	
N/0109	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/10/2021	12/11/2021	PL	
N/0108	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2021	12/11/2021	PL	
WS/1948	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	12/11/2020	12/11/2021	SmPC and PL	
T/0106	Transfer of Marketing Authorisation	03/04/2020	02/06/2020	SmPC, Labelling and PL	
N/0105	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/03/2020	02/06/2020	PL	
WS/1741	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test	16/01/2020	n/a		

	procedure is already authorised				
N/0104	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/11/2019	02/06/2020	PL	
WS/1464/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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.7 - Administrative change - Deletion of manufacturing sites B.I.z - Quality change - Active substance - Other variation	23/05/2019	n/a		
N/0102	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/05/2019	24/10/2019	PL	
N/0101	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/03/2019	24/10/2019	PL	
WS/1460	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	29/11/2018	24/10/2019	SmPC	

	Veterinary Medicinal Products - Other variation				
T/0098	Transfer of Marketing Authorisation	11/07/2018	30/07/2018	SmPC, Labelling and PL	
N/0097	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/10/2017	30/07/2018	Labelling	
PSUSA/2699/ 201612	Periodic Safety Update EU Single assessment - sildenafil (indicated for erectile dysfunction)	01/09/2017	n/a		PRAC Recommendation - maintenance
IA/0096/G	This was an application for a group of variations. B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised B.II.d.2.z - Change in test procedure for the finished product - Other variation	10/08/2017	n/a		
IB/0094/G	This was an application for a group of variations. 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 B.II.a.3.a.1 - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system -	28/04/2017	n/a		

	Addition , deletion or replacement B.II.a.3.a.2 - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Increase or reduction B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation				
N/0093	Update of the package leaflet with revised contact details of the local representative for Germany. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/06/2016	09/01/2017	PL	
IB/0092/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	10/06/2016	n/a		
IB/0091	B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation	29/01/2016	09/01/2017	SmPC and PL	
IB/0090	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/10/2015	22/01/2016	SmPC, Annex II and PL	
N/0088	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	23/09/2015	PL	

IB/0089	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/06/2015	23/09/2015	SmPC	
IB/0087/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	27/04/2015	23/09/2015	SmPC, Labelling and PL	
IA/0086	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	20/01/2015	n/a		
IAIN/0085	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	23/10/2014	23/09/2015	Annex II and PL	
PSUSA/2699/ 201312	Periodic Safety Update EU Single assessment - sildenafil (indicated for erectile dysfunction)	11/09/2014	n/a		PRAC Recommendation - maintenance
N/0084	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/08/2014	23/09/2015	PL	
II/0082	Update of section 4.8 of the SmPC in order to update frequency and frequency categories of all ADRs	20/03/2014	14/07/2014	SmPC and PL	The MAH performed a re-evaluation of the extended clinical database analysing 74 double blind placebo control studies

	based upon all casualty adverse events and to rank in decreasing order of severity the preferred terms within the same System Organ Class. The MAH also updated the SOC eye disorders ADRs in section 4.8 of the SmPC. The package leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				which determined the update of the frequency and frequency category of the Adverse Drug Reactions (ADRs) in the Summary of Product Characteristics and Package Leaflet accordingly. No AE terms have been deleted; 12 new ADRs (Abdominal pain upper, Feeling hot, Gastrooesophageal reflux disease, Hot flush, Hypoaesthesia oral, Irritability, Nasal dryness, Nasal oedema, Pain in extremity, Rhinitis, Sinus congestion, and Throat tightness) have been added and System Organ Classification (SOC) for Eye Disorder has been further specified with more specific preferred terms regarding eye disorders.
II/0080	Update of Section 4.5 of the SmPC to add new drug-drug interaction based on data from study A1481149 and to revise information regarding drug-drug metabolic interaction which may affect sildenafil metabolism. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/01/2014	14/07/2014	SmPC	Data derived from pharmacological analysis of a drug-drug interaction study indicated that an inducer of metabolic enzyme (CYP3A4), bosentan, reduces steady state level of regularly administered Viagra. Therefore this variation is including this information under the section 4.5 "Interaction with other medicinal products and other forms of interaction" of the Summary of Product Characteristics (SmPC). Furthermore, better specification of Erythromycin as moderate CYP3A4 inhibitor has been implemented in section 4.5 of the SmPC, as well as information on possible effect of inducers of cytochrome P450 on pharmacokinetic parameter of Viagra.
II/0079	Update of section 4.4 of the Viagra SPC to include additional information regarding priapism and potential risk effects of exceeding the recommended dose for concomitant use of Viagra with other Sildenafil containing products or other PDE5 inhibitors. The package leaflet is updated accordingly.	23/01/2014	14/07/2014	SmPC and PL	A cumulative review on Viagra use and event of erection increased, painful erection and priapism identified a total of 2,862 cases. Priapism is already stated in the section 4.8 of the SmPC with a frequency "unknown". Within this variation, based on the review presented, information that prolonged erections and priapism have been reported with sildenafil in postmarketing experience was added in section

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				4.4 of the SmPC, together with a recommendation to seek immediate medical assistance if this occur. Furthermore, section 4.4 has been updated to not recommend the combinations of sildenafil with other PDE5 Inhibitors, or other pulmonary arterial hypertension (PAH) treatments containing sildenafil (REVATIO) as the safety and efficacy of these combinations have not been studies.
IB/0081	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/01/2014	n/a		
II/0078	Update of the section 4.4 of the SmPC to revise the information on acute NAION based on new data coming from the clinical study A1481259 (MEA16.9 and 16.10). The applicant has taken the occasion to update the PI following the latest requirement for QRD v9. Update to add Croatian local representative has been introduced in the PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/07/2013	14/07/2014	SmPC, Annex II and PL	Assessment of an observational clinical study, "Case-Crossover Study of PDE5 Inhibitor Exposure as a Potential "Trigger Factor" for Acute NAION", indicates a higher association of risk for the rare condition of Non-arteritic Anterior Ischaemic Optic Neuropathy in the population using PDE5i. The estimated risk is approximately 2 fold increased within 5 half-lives of PDE5i use and using a conservative assumptions on annual incidence estimates, PDE5i use is estimated to add 3 to 8 cases per 100,000 males 50 years and older per year. On this basis, the section 4.4 "Special warnings and precautions for use" has been updated to include the results from this study.
II/0076/G	This was an application for a group of variations. This was an application for a group of variations: - To add an alternative manufacturing process of the drug substance. - To add new specification parameters to the specifications of an Intermediate used during the	30/05/2013	n/a		

	manufacturing process of the active substance. - To add a new test procedure for the Starting materials and Intermediates used during the manufacturing process of the active substance. - To change the specifications of the active substance. - To change the test procedures for the active substance. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product 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 B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate 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 B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement				

	or addition) for the AS or a starting material/intermediate				
X/0070	Annex I_2.(d) Change or addition of a new pharmaceutical form	21/02/2013	17/04/2013	SmPC, Annex II, Labelling and PL	Please refer to the assessment report Viagra-H-C-000202-X-0070-AR
IB/0077/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.z - Change in test procedure for the finished product - Other variation B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	26/03/2013	n/a		
II/0073	Update of section 4.8 of the SmPC following FUM 028 assessment, in order to update the safety information adding Penile haemorrhage,	13/12/2012	17/04/2013	SmPC and PL	The present variation acknowledge the request from the CHMP to update the safety information of the product on urogenital bleeding Adverse Drug Reactions as indicated by

	Haematospermia, and Haematuria with an uncommon frequency. 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 update the list of local representatives for Greece and Cyprus in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				the assessment for the cumulative overview required and assessed during previous procedure started by an identified an validated signal from EMA. Following the assessment of the cumulative overview, concerning the role of sildenafil for urogenital bleeding events, it has been concluded that there is sufficient evidence for a possible relationship between sildenafil and penile haemorrhage, haematospermia and haematuria. This mainly related to a possible association of sildenafil use with the above mentioned ADRs in the analysis of post marketing exposure and data part of the FDA AERS and company safety database. This possible association of the urogenital bleeding ADRs have been furthermore related also to other PDE5 inhibitor class of active substances, to which sildenafil belongs. As a result of this assessment the MAHs for Viagra has been asked the introduction of Penile haemorrhage, Haematospermia, and Haematuria to Section 4.8 of the SmPC.
IG/0236/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	03/12/2012	n/a		
IA/0074	B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction	23/10/2012	n/a		

IB/0072	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	03/07/2012	n/a		
IA/0071	A.7 - Administrative change - Deletion of manufacturing sites	22/05/2012	n/a		
IA/0069/G	This was an application for a group of variations. B.II.e.3.c - Change in test procedure for the immediate packaging of the finished product - Deletion of a test procedure if an alternative test procedure is already authorised B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure	15/12/2010	n/a		
IB/0068	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	29/11/2010	n/a		
IB/0067	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	12/08/2010	n/a		
II/0064	Update of section 4.8 of the Summary of Product Characteristics to include severe cutaneous adverse drug reactions, i.e. Stevens Johnson syndrome and Toxic epidermal necrolysis, as recommended by the CHMP further to the assessment of FUM 022. The Package Leaflet is amended accordingly. In addition,	20/05/2010	01/07/2010	SmPC and PL	A cumulative review of the available post-marketing experience through to 17 May 2009 for severe cutaneous adverse drug reactions i.e. Stevens Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) has been performed. There were 6 cases for which a possible relation between the occurrence of these events and the use of

	the web address of the EMA has been updated in Section 10 of the SmPC and in the PL. Update of Summary of Product Characteristics and Package Leaflet				sildenafil cannot be excluded. Hence, section 4.8 of the SmPC has been updated to include SJS and TEN.
IA/0065	To change the name of a manufacturer from Heinrich Mack Nachfolger GmbH & Co. KG to Pfizer Manufacturing Deutschland GmbH. 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)	26/05/2010	n/a		
II/0063	Change in the testing procedure during the manufacturing process of the finished product. Quality changes	18/03/2010	23/03/2010		
IA/0062	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	21/09/2009	n/a		
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/08/2009	n/a	Labelling	
IB/0058	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	15/06/2009	n/a		
N/0057	Update of the local representative details for Germany in section 6 of the Package Leaflet.	29/01/2009	n/a	PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
R/0052	Renewal of the marketing authorisation.	26/06/2008	26/08/2008	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the 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 Viagra continues to be favourable. The CHMP was also of the opinion that the renewal can be granted with unlimited validity.
IA/0056	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	01/04/2008	01/04/2008	SmPC, Labelling and PL	
IA/0055	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	01/04/2008	01/04/2008	SmPC, Labelling and PL	
IA/0054	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	01/04/2008	01/04/2008	SmPC, Labelling and PL	
IA/0053	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	01/04/2008	01/04/2008	SmPC, Labelling and PL	
II/0051	Update to section 4.8 of of Summary of Product Characteristics to include sudden deafness. The package leaflet is amended accordingly.	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

	Update of Summary of Product Characteristics and Package Leaflet				provided, the CHMP recommended that the term "sudden deafness" be included in section 4.8 of the SPC for all PDE5 inhibitors including Viagra (sildenafil).
IA/0050	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	16/01/2008	n/a		
IA/0049	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	16/01/2008	n/a		
IA/0048	IA_47_c_Deletion of a pack size(s)	20/11/2007	n/a	SmPC, Labelling and PL	
IA/0047	IA_47_c_Deletion of a pack size(s)	20/11/2007	n/a	SmPC, Labelling and PL	
IA/0046	IA_47_c_Deletion of a pack size(s)	20/11/2007	n/a	SmPC, Labelling and PL	
N/0035	Update of the local representatives contact details in section 6 of the Package Leaflet for Bulgaria, Ireland, Latvia, Netherlands, Romania and Slovakia. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/11/2007	n/a	PL	
IB/0041	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	07/11/2007	n/a		
IA/0040	IA_04_Change in name and/or address of a manuf.	16/10/2007	n/a		

	of the active substance (no Ph. Eur. cert. avail.)				
IA/0039	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	15/10/2007	n/a		
IA/0038	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	10/10/2007	10/10/2007	SmPC, Labelling and PL	
IA/0037	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	10/10/2007	10/10/2007	SmPC, Labelling and PL	
IA/0036	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	10/10/2007	10/10/2007	SmPC, Labelling and PL	
IA/0033	IA_13_a_Change in test proc. for active substance - minor change IA_20_a_Change in test procedure for an excipient - minor change to approved test procedure	19/09/2007	n/a		
IA/0032	IA_13_a_Change in test proc. for active substance - minor change IA_20_a_Change in test procedure for an excipient - minor change to approved test procedure	19/09/2007	n/a		
IA/0031	IA_13_a_Change in test proc. for active substance - minor change IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	19/09/2007	n/a		

IA/0030	IA_13_a_Change in test proc. for active substance - minor change	05/07/2007	n/a		
IB/0029	IB_33_Minor change in the manufacture of the finished product	27/02/2007	n/a		
N/0028	The Marketing Authorisation Holder (MAH) applied for the inclusion of the Romanian and Bulgarian local representatives in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/02/2007	n/a	PL	
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/12/2006	n/a	Labelling and PL	
II/0026	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 local representatives in Poland and Sweden have been amended and the MAH took the opportunity to update the Product Information in accordance to QRD template version 7.	27/04/2006	08/06/2006	SmPC, Annex II, Labelling and PL	In the context of the ongoing evaluation of the NAION issue (see II-25) 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 sildenafil 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

	Update of Summary of Product Characteristics, Labelling and Package Leaflet				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 sildenafil and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking VIAGRA 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. In addition, the Product Information was updated to reflect requirements of the new legislation.
II/0025	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 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 minor linguistic and QRD changes were added to Product Information. The labelling for the different presentations has been combined and the local representatives in Latvia, Greece and Poland have been updated. A warning statement on lactose was also included.	13/10/2005	15/11/2005	SmPC, Labelling 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 in the 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

	Update of Summary of Product Characteristics, Labelling and Package Leaflet				are likely to be present in the population exposed to these drugs, has made it difficult to draw any firm conclusion on 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 sildenafil. Other articles describe cases of NAION after use of sildenafil. 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 (including a case for the Prescription Event Monitoring (PEM study). 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 each of the three PDE5 inhibitors is below the backgrou
II/0024	This Variation relates to changes to the Summary of Product Characteristics (SPC) sections 4.2 (Posology and method of administration), 4.4 (Special warnings and special precautions for use) and 4.5 (Interaction with other medicinal products and other forms of interaction) to include information on the potential interaction between sildenafil and alpha blockers following a reevaluation of the original data and the completion of a sildenafil-doxazosin interaction	16/03/2005	27/04/2005	SmPC, Labelling and PL	Further to the 2 studies submitted for the procedure II/018, the MAH provided the result of a third study (A1481163) which investigated the effects of a single dose of sildenafil (100 mg) in subjects with benign prostatic hyperplasia being treated with doxazosin (=4 mg).The co-administration of sildenafil had no clinically relevant effects on the pharmacokinetsics of doxazosin. Regarding the pharmacodynamic changes, the observed reduction in blood pressure appear additive in nature, as expected.

	clinical trial study. Corresponding changes have been introduced in section 2 of the Package Leaflet (PL). The list of local representatives in the PL has been updated and QRD related changes introduced in the SPC, labelling and PL. Some minor linguistic changes are included in the German, Lithuanian, Spanish, French, Portuguese and Hungarian texts. Update of Summary of Product Characteristics, Labelling and Package Leaflet				Overall, it can be concluded that the combination of sildenafil with doxazosin (=4 mg) is generally well tolerated provided that the patient is already stable on the doxazosin dose and that the sildenafil administration starts with a low dose. This is reflected in the SPC and PL.
IA/0023	IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	20/08/2004	n/a	SmPC	
II/0020	This variation concerns an update of section 4.2 of the Summary of Product Characteristics (SPC) to change the starting dose in the elderly population. Corresponding changes have been introduced in section 2 of the Package Leaflet (PL). Section 4.5 of the SPC is also updated to include information on the potential interaction between nicorandil and sildenafil. Update of Summary of Product Characteristics and Package Leaflet	24/03/2004	26/05/2004	SmPC and PL	The MAH applied for an update to change the starting dose in the elderly population. At the time of the original EU marketing authorisation application it was considered appropriate to recommend a 25 mg starting dose for the elderly on the grounds that experience was limited and also that pharmacokinetic data had shown that healthy elderly volunteers (65 years or over) had reduced clearance of sildenafil. In most studies the MAH has conducted since the initial registration a starting dose of 50 mg had been chosen both in patients with an age < 65 years and with an age 3 65 years (n = 2903 and 679, respectively) and a comparison was submitted both with placebo and with a starting dose

					of £ 25 mg and 100 mg. Based on the data submitted the CPMP concluded that data in the elderly support a starting dose of 50 mg. In addition, it was demonstrated that a 50 mg starting dose of sildenafil in patients aged = 65 years is tolerated well without differences in percentages of adverse events compared to younger patients. Therefore the CPMP concluded that no specific dosing considerations have to be given in elderly patients. These conclusions were reflected in updates to sections 4.2 of the SPC and section 2 of the Package Leaflet.
IB/0022	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	02/02/2004	n/a		
IB/0021	IB_31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits	21/01/2004	n/a		
R/0019	Renewal of the marketing authorisation.	24/07/2003	11/11/2003	SmPC, Annex II, Labelling and PL	
II/0018	This variation relates to an update of section 4.5 of the SPC and the corresponding section 2 of the PL to account for the possible interaction of sildenafil with alpha-blockers. In addition, the sentence "Not all packages may be marketed" is added to section 6.5 of the SPC. SPC section 6 of the PL is updated Update of Summary of Product Characteristics and Package Leaflet	25/04/2003	29/07/2003	SmPC and PL	The MAH applied for an update to reflect the possible interaction of sildenafil with alpha-blockers. The MAH submitted the results of two clinical studies (study 148-242 and A1481068) and a publication. Study 148-242 investigated the effects of a single dose of sildenafil (100 mg in 4 subjects who were recruited to Part 1, and 25 mg in 17 subjects who were recruited to Part 2) on blood pressure and pulse rate in subjects with benign prostatic

					hyperplasia being treated with doxazosin (= 4 mg) once daily. Study A1481068 investigated the effects of a single dose of sildenafil (50 mg) on blood pressure and pulse rate in subjects with benign prostatic hyperplasia being treated with doxazosin (= 4 mg) once daily. Both studies were double-blind, placebo-controlled, randomised and two-way crossover studies. The publication submitted was by De Rose et al, 'Combined oral therapy with sildenafil and doxazosin for the treatment of non-organic erectile dysfunction refractory to sildenafil monotherapy', Int. J. of Impotence Research (2002)14, 50-53. The studies showed an additional blood pressure reduction with sildenafil compared to placebo. There were several reports of the adverse events 'hypotension' and 'dizziness' classified as treatment-related in the sildenafil/doxazosin group, whereas no such reports were obtained in the placebo/doxazosin group. The extent of the additional blood pressure lowering effect in the individual patients who received doxazosin and the 100 mg sildenafil dose compared to doxazosin/placebo, suggests a pharmacodynamic interaction beyond the blood pressure lowering effect of sildenafil itself (as indicated in Section 5.1 of the SPC-text). The exact mechanism remains unclear, but it is probably due to potentiation of the vascular effects of both drugs. A precaution was therefore added to section 4.4 of the SPC that Viagra should be used with caution in users of alpha-blockers as simultaneous co-administration may lead to symptomatic hypote

I/0017	25_Change in test procedures of the medicinal product	06/03/2003	11/03/2003		
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/11/2002	04/12/2002	PL	
I/0015	01_Change in the name of a manufacturer of the medicinal product	08/10/2002	24/10/2002	Annex II and PL	
II/0013	Update of section 5.1 of the Summary of Product Characteristics (SPC) and Package Leaflet with regards to data available from new publications and studies in patients with severe coronary artery disease and in patients with erectile dysfunction and stable angina. Update of Summary of Product Characteristics and Package Leaflet	17/01/2002	18/04/2002	SmPC and PL	
I/0012	20_Extension of shelf-life as foreseen at time of authorisation	09/11/2001	05/03/2002	SmPC	
II/0011	Update of Summary of Product Characteristics	26/07/2001	27/11/2001	SmPC	
I/0010	11a_Change in the name of a manufacturer of the active substance	27/03/2001	n/a	Annex II	
I/0008	20_Extension of shelf-life as foreseen at time of authorisation	28/09/2000	07/12/2000	SmPC	
I/0007	11b_Change in supplier of an intermediate	28/09/2000	n/a		

	compound used in manufacture of the active substance				
II/0006	Update of Summary of Product Characteristics, Labelling and Package Leaflet	25/05/2000	12/09/2000	SmPC, Labelling and PL	
I/0005	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	23/02/2000	n/a		
II/0004	Update of Summary of Product Characteristics and Package Leaflet	21/10/1999	10/02/2000	SmPC and PL	
I/0003	20_Extension of shelf-life as foreseen at time of authorisation	08/09/1999	14/12/1999	SmPC	
I/0002	13_Batch size of active substance	08/09/1999	n/a		
II/0001	Update of Summary of Product Characteristics and Package Leaflet	22/04/1999	09/08/1999	SmPC and PL	