Jalra

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/3113/ 202402	Periodic Safety Update EU Single assessment - vildagliptin, metformin / vildagliptin	03/10/2024	n/a		PRAC Recommendation - maintenance
IG/1745	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	17/04/2024	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).

WS/2590	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.z - Quality change - Active substance - Other variation	18/01/2024	n/a		
WS/2524	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	12/10/2023	n/a		
IG/1652/G	This was an application for a group of variations. 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 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)	14/08/2023	29/07/2024	Annex II and PL	
IG/1583	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	19/12/2022	n/a		

WS/2283/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.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF 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	06/10/2022	n/a		
WS/2253	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 new ADRs 'cutaneous vasculitis' with the frequency “not known”. 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	07/07/2022	17/07/2023	SmPC and PL	
WS/2224	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	23/06/2022	17/07/2023	SmPC and PL	For more information, please refer to the Summary of Product Characteristics

	Update of section 4.8 of the SmPC in order to update the list of ADRs and update the ADR table in line with the SmPC guideline (a recommendation of EMEA/H/C/WS1970). The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
N/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/05/2022	15/07/2022	PL	
WS/2221/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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	17/03/2022	n/a		
PSUSA/3113/ 202102	Periodic Safety Update EU Single assessment - vildagliptin, metformin / vildagliptin	28/10/2021	n/a		PRAC Recommendation - maintenance

IG/1445	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	20/10/2021	n/a		
WS/1970	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of an updated RMP (version 15.2) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and aligned with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00003113/201802) adopted in October 2018. Annex II.D of the product information is updated to remove the statement around submission of an RMP update every 3 years. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	30/09/2021	15/07/2022	Annex II	
WS/2108/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.c.1.a - Change in immediate packaging of the AS	02/09/2021	n/a		

	- Qualitative and/or quantitative composition 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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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.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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IG/1421/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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 A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the	21/07/2021	15/07/2022	Annex II and PL	

	finished product, including quality control sites (excluding manufacturer for batch release)				
IG/1407/G	This was an application for a group of variations. B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	23/06/2021	n/a		
WS/1938/G	This was an application for a group of variations following a worksharing procedure according to	20/05/2021	21/06/2021	SmPC	Please refer to Scientific Discussion ‘Galvus_Jalra_Xiliarx-H-

	Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.1, 5.1 and 6.6 of the SmPC to change the existing indication with regards to the use in combination with other diabetes medicines and to include VERIFY study data (on initial combination of vildagliptin with metformin). The Package Leaflet is updated in accordance. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				C-WS-1938-G’
IG/1322	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	16/12/2020	n/a		
WS/1907/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.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a	01/10/2020	18/12/2020	SmPC, Annex II and PL	

	manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IG/1185	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	20/12/2019	18/12/2020	Annex II and PL	
WS/1658/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.	12/09/2019	n/a		

	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.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.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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size 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 originally approved batch size B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation				

	B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition				
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/02/2019	18/12/2020	PL	
WS/1513	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	17/01/2019	n/a		
N/0062	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/11/2018	18/12/2020	PL	
PSUSA/3113/ 201802	Periodic Safety Update EU Single assessment - vildagliptin, metformin / vildagliptin	04/10/2018	n/a		PRAC Recommendation - maintenance
IG/0979/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.c - Change in the specification parameters	10/09/2018	n/a		

	and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IG/0942	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	26/06/2018	n/a		
IG/0943	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	01/06/2018	n/a		
IG/0928/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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	03/05/2018	n/a		

	of the AS				
IG/0920/G	This was an application for a group of variations. 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.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.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.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	26/04/2018	n/a		
T/0055	Transfer of Marketing Authorisation	26/03/2018	26/04/2018	SmPC, Labelling and PL	
IG/0895	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	21/02/2018	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IG/0843/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.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.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	04/10/2017	n/a		
WS/1072	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 5.1 of the SmPC, subsection 'cardiovascular risk', with results from a new meta-analysis evaluating the cardiovascular safety of vildagliptin. In addition, the Worksharing applicant (WSA) took the opportunity to bring the annexes in	21/04/2017	01/03/2018	SmPC, Annex II, Labelling and PL	A meta-analysis of independently and prospectively adjudicated cardiovascular events from 37 phase III and IV monotherapy and combination therapy clinical studies of up to more than 2 years duration (mean exposure 50 weeks for vildagliptin and 49 weeks for comparators) was performed and showed that vildagliptin treatment was not associated with an increase in cardiovascular risk versus comparators. The composite endpoint of adjudicated major adverse cardiovascular events (MACE) including acute

	line with the latest QRD template version 10, and to merge the two SmPCs into one single SmPC for Eucreas, Icandra and Zomarist. Moreover, the section on pregnancy and breast-feeding in the PL for Eucreas/Icandra/Zomarist has been aligned with the wording used for Galvus/Jalra/Xiliarx. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				myocardial infarction, stroke or cardiovascular death was similar for vildagliptin versus combined active and placebo comparators [Mantel–Haenszel risk ratio (M-H RR) 0.82 (95% CI 0.61 1.11)]. A MACE occurred in 83 out of 9,599 (0.86%) vildagliptin-treated patients and in 85 out of 7,102 (1.20%) comparator-treated patients. Assessment of each individual MACE component showed no increased risk (similar M-H RR). Confirmed heart failure (HF) events defined as HF requiring hospitalisation or new onset of HF were reported in 41 (0.43%) vildagliptin-treated patients and 32 (0.45%) comparator-treated patients with M-H RR 1.08 (95% CI 0.68 1.70).
WS/1088	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	21/04/2017	n/a		
IG/0786	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/03/2017	01/03/2018	SmPC	
WS/1094/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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/02/2017	n/a		

	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test				
IG/0713/G	This was an application for a group of variations. 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) A.7 - Administrative change - Deletion of manufacturing sites	14/07/2016	n/a		
N/0046	Update of the package leaflet with revised contact details of the local representatives for Greece and Germany. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/03/2016	01/03/2018	PL	
WS/0791	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/01/2016	n/a		

PSUSA/3113/ 201502	Periodic Safety Update EU Single assessment - vildagliptin, metformin / vildagliptin	22/10/2015	16/12/2015	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3113/201502.
IG/0637	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	02/12/2015	n/a		
IG/0566/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction	02/06/2015	n/a		
WS/0722	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 line with a PRAC recommendation dated 4 Dec 2014, in order to add the ADR 'myalgia' with frequency "not known". The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representative in Spain in the Package Leaflet for Xiliarx and Icandra.	21/05/2015	16/12/2015	SmPC and PL	N/A

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/0547	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	27/04/2015	n/a		
WS/0696	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update the RMP to version 12.1 by changing the due date of the final CSR report for Study CLAF237A2401 from 'Q4 2014' to 'Q2 2015'. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	26/02/2015	n/a		
IG/0508	A.1 - Administrative change - Change in the name and/or address of the MAH	28/11/2014	24/04/2015	SmPC, Labelling and PL	
WS/0584/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. This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No	24/07/2014	n/a		

	1234/2008. 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.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.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.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.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.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.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.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.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.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.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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of				

	specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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.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.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				
IG/0459	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	14/07/2014	n/a		

WS/0540/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. To add a new specification parameter to the finished product release specification. To delete a specification parameter from the finished product shelf-life specification. To tighten a specification parameter of the finished product release specification. To delete a specification parameter from the finished product release specification. To add an alternative microbial method to the specifications of the finished product. To introduce minor changes to test procedures for the finished product. To update a test procedure for the finished product to comply with a general monograph in the Ph. Eur. B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a	25/04/2014	n/a		

	non-significant specification parameter B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.2.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.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.e - Change in test procedure for the finished product - Update of the test procedure to comply with the updated general monograph in the Ph. Eur. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
WS/0518	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 update the safety information on acute pancreatitis. The Package Leaflet was updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/04/2014	24/04/2015	SmPC, Labelling and PL	The MAH has provided information on clinical studies that may provide further safety data with regards to pancreatic safety in patients treated with vildagliptin. In the absence of a CV outcome study, the VERIFY study is discussed. This study is relatively small (2000 patients) when it comes to investigating uncommon events but instead of long duration (5 years). Adverse events will be captured with routine methods in the study with specific analyses of pancreatic events which is considered sufficient. Timelines have been provided and are acceptable. The MAH has also provided information on the only observational study currently ongoing and planned. The

					study protocol already includes pancreatitis as an outcome of interest and the protocol has been amended with pancreatic cancer. The updated protocol is included in the updated RMP. The benefit/risk balance for Galvus/Eucreas remains positive.
IG/0398/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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	24/01/2014	n/a		
R/0031	Renewal of the marketing authorisation.	19/09/2013	28/11/2013		
WS/0358	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 4.4 and 5.1 of the SmPC in order to include data in patients with type 2 diabetes mellitus and congestive heart failure NYHA class I-III. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.	27/06/2013	31/07/2013	SmPC, Annex II and PL	With the current variation new clinical data in patients with T2DM and CHF NYHA class I-III has been provided. Based on previously available data, the use of vildagliptin in patients with CHF in NYHA class I-II has been accepted, whereas the use of vildagliptin in patients with CHF in NYHA class III-IV has not been recommended due to lack of data. The number of patients in NYHA class III treated with vildagliptin is still limited (47) and the data indicate that there were imbalances with regards to background morbidity, thus the data has to be interpreted with caution and the data are insufficient to make claims on the efficacy and safety of vildagliptin in this patient group.

	Furthermore, the PI is being brought in line with the latest version of the QRD template. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				In the study submitted, the primary objective was to investigate the effect of vildagliptin on cardiac safety with change in LVEF being the primary outcome. The data on LVEF, as well as on worsening of CHF does not indicate any adverse effect of vildagliptin on cardiac function and there is no mechanistic/biological rationale for a negative effect. There were, however, imbalances in AE reporting with more SAEs and deaths observed in the vildagliptin treated NYHA class III population. This was most likely related to the background morbidity. The safety data from the study is in line with the known safety profile of vildagliptin. However, data in patients with CHF NYHA III is still limited and this issue will be continuously monitored in future PSURs which is endorsed. The outcome with regards to HbA1c, responder analysis and FPG in the overall study population (CHF, NYHA class I-III) was in line with that observed in previous studies with vildagliptin although the effect was less prominent at week 52. In patient with CHF, NYHA class III, the HbA1c was modest (-0.3 %), however, this subgroup of patients was small and there are indications of heterogeneity in the data which may explain the modest reduction in HbA1c. This was reflected in the study description in section 5.1 of the SmPC. Due to the limited number of patients, the data provided is still deemed insufficient to decide on the overall benefit risk balance of vildagliptin in patients with CHF NYHA class III. The submitted study, which focused on changes in LVEF in patients treated with vildagliptin, however, provides sufficient data to allow a cautious use in these patients support that vildagliptin has no negative effect on cardiac function and there is no mechanistic/biological rationale for

					such an effect. The benefit-risk balance for vildagliptin containing products remains positive.
IB/0032/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	24/07/2013	n/a		
WS/0345/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. - To add a manufacturer of a starting material. - To delete two manufacturing sites for a starting material. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of	17/01/2013	17/01/2013		

	manufacturing sites				
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
WS/0272	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication for the use of vildagliptin and vildagliptin/metformin in triple therapy with a sulphonylurea and metformin affecting sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC. The Package Leaflet was proposed to be updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/09/2012	29/10/2012	SmPC and PL	For further information please refer to the scientific conclusion: H-XXX-WS-0272-AR
WS/0257	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This was an application for a variation following a	20/09/2012	29/10/2012	SmPC and PL	For further information please refer to the scientific conclusion: H-XXX-WS-0257-AR

	worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication for use of vildagliptin and vildagliptin/metformin in combination with insulin affecting sections 4.1, 4.2, 4.8 and 5.1 of the SmPC. The Package Leaflet is updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IG/0209/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details 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	17/08/2012	n/a		
WS/0256	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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 4.4 and 4.8 of the	24/05/2012	28/06/2012	SmPC and PL	At the time of granting marketing license, skin lesions were considered a potential risk based on pre-clinical findings in monkeys. In the assessment of the PSUR No 7 of Galvus, 19 post marketing reports of blistering dermatitis, bullous rash pemphigus were identified. Of these, a causal association to vildagliptin was suspected in 9 cases. To further evaluate the possible risk of skin adverse reactions associated with vildagliptin, the MAH was requested to

	SmPC in order to add a warning of bullous or exfoliative skin lesions following the review of the Galvus PSUR 7. The Package Leaflet is updated accordingly. C.I.3.z - 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 - Other variation. C.I.3.z - 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 - Other variation				submit a thorough evaluation of all relevant cases. This evaluation concluded that "bullous or exfoliative lesions" should be added to the description of the post-marketing experience of sections 4.4 and 4.8 of the SmPC.
WS/0140/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. To include an additional manufacturing site and a quality control site for the drug product . To make some changes in the manufacturing process of the drug product. B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid	19/04/2012	19/04/2012		

	oral dosage form or oral solutions B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection				
IG/0148/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	22/02/2012	n/a		
WS/0187	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 4.1 and 4.2 of the SmPC in order to include monotherapy indication for vildagliptin. In addition, section 4.4 has been updated by deleting warning of cautious use of vildagliptin in patients with congestive heart failure of NYHA functional class I-II. The Package Leaflet is updated in accordance.	15/12/2011	31/01/2012	SmPC and PL	The Scientific discussion of the CHMP Assessment Report will be published.

	Furthermore, the PI is being brought in line with the latest QRD template version 8.0. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IG/0141/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	25/12/2011	n/a		
IB/0021	B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	13/12/2011	n/a		
WS/0149	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 4.4, 5.1 and 5.2 of the SmPC based on the results of studies in patients with moderate and severe renal impairment and end stage renal disease (ESRD). The PL is amended accordingly.	20/10/2011	24/11/2011	SmPC and PL	During the review of the original Marketing Authorisation application for vildagliptin, there was limited experience in patients with moderate and severe renal impairment and End Stage Renal Disease (ESRD). The company committed to conduct additional studies to evaluate the pharmacokinetics, efficacy and safety of vildagliptin in this patient population. Following this commitment, the MAH has performed two clinical safety trials in patients with moderate and severe impaired renal

	This application was submitted for a group of variations consisting of a Type II variation following a worksharing procedure according to 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				function. In parallel the company has also performed two additional clinical pharmacology studies in subjects with varying degrees of renal impairment. These data in patients with moderate and severe renal impairment and ESRD are discussed in the present submission. Data in patients with end stage renal disease is very limited. Evaluation of concentrations taken in patients on dialysis suggests that vildagliptin and BQS867 (a minor metabolite of vildagliptin excreted <10% in plasma and <5% in urine) concentrations were of a similar magnitude in patients with ESRD and patients with severe renal impairment. Hence, the safety data obtained in patients with severe renal impairment would cover the exposure of vildagliptin and BQS867 also in ESRD patients. Regarding LAY151 (major human metabolite of vildagliptin), the plasma concentrations in ESRD are about three-fold higher than in patients with severe renal impairment. As AUC in severe renal impairment was about 7-fold higher than in patients with normal renal function, the exposure to LAY151 will be considerably higher in ESRD patients than in patients with normal renal function (with a dose reduction to 50 mg q.d. in ESRD) and also higher than in patients with severe renal impairment where safety has been shown. It is acknowledged that LAY151 is pharmacologically inactive and has not been associated with organ toxicity during the original application. However, it is not fully clear if the exposure obtained in ESRD patients have been covered in the toxicity studies. As there is limited experience in this patient population, a cautionary statement was added to section 4.4 of the SmPC. It is acknowledged that treatment alternatives in ESRD patients

					are limited and it can be agreed that vildagliptin can be used with caution in ESRD patients. The clinical data provided in patients with moderate and severe renal impairment indicate that there is neither a loss of efficacy nor an exaggerated response to vildagliptin in this population with the proposed adjusted dose. In one of the submitted studies vildagliptin was used as add-on therapy in patients with moderate to severe renal impairment, who were mainly on an insulin based treatment (80% in the study). The results of efficacy have been presented according to baseline treatment (insulin or non-insulin therapy) and no apparent difference in outcome was observed between groups. The mean total insulin dose was only marginally changed from baseline to end of study and no apparent differences were observed between vildagliptin and placebo/comparator treated groups. The safety data has limitations due to the small size of the studies which preclude evaluation of uncommon adverse events. The inclusion of both placebo and active control, however, gives some reassurance in the evaluation. The overall adverse event pattern does not appear to be different in this population as compared to the overall type 2 diabetes population. No firm conclusions can be drawn regarding the uncommon adverse event of interest, but the data does not indicate that renally impaired patients are more prone to develop the specific adverse events identified as known or potential risks with vildagliptin treatment. In view of these data, the CHMP agreed that vildagliptin could be recommended for use in patients with moderate and severe renal impairment at a reduced dose. It also agreed that vildagliptin can be used with caution at a

					reduced dose in ESRD patients.
WS/0125	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of product information with data on liver dysfunction received by the MAH from marketed use of vildagliptin. In addition, the MAH took the opportunity to update the list of local representatives 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	20/10/2011	24/11/2011	SmPC and PL	The clinical safety database for vildagliptin consists of pooled analysis of data from 38 clinical trials including more than 11,500 patients treated with vildagliptin. Furthermore, post-marketing data are available from more than 1.24 million patient years. Data from clinical trials, although not statistically significant, indicate a slightly increased risk of persistent transaminase elevation in patients treated with vildagliptin relative to the comparators. This risk is reflected in the current labeling. Following a request by the CHMP (EMA/549257/2010), the MAH has conducted an evaluation of all reports related to liver dysfunction received from marketed use of vildagliptin (including Galvus and Eucreas) since the original placing on the market. The cumulative post-marketing experience has identified seven cases consistent with a drug-related liver event and a further 15 cases where a causal association cannot be excluded. Based on this, the CHMP considered that the safety information referring to the post-marketing experience in section 4.8 should be updated to reflect this safety concern. Additionally, the MAH agreed to the CHMP request that adverse liver events should be reviewed again in future PSURs.
WS/0164	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	22/09/2011	27/10/2011	SmPC and PL	Following the review of the latest vildagliptin PSUR, the CHMP requested the addition to the SmPC of a warning statement on acute pancreatitis including information that

	Update of Section 4.4 of the SPC and relevant section of the PL to include a warning on pancreatitis, following assessment of the latest PSUR. 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				patients should be informed on the characteristic symptoms of acute pancreatitis, that resolution has been observed after discontinuation and that treatment should not be resumed after pancreatitis has been diagnosed. Few cases of pancreatitis were reported in the clinical trials safety data base and there was no apparent imbalance between vildagliptin and comparators/placebo. In five of the cases the pancreatitis occurred in the context of cholelithiasis or cholecystitis and all the four cases in which vildagliptin was re-initiated belonged to this group. That is, all the rechallenged cases had an easily identifiable risk factor for pancreatitis present and all four rechallenges were negative. The post-marketing data presented with the current variation covers the period up to 30 April 2011. The cut-off date for the latest PSUR was 30 Nov 2010, thus the current report covers an additional time period of five months. Overall, the analysis of post-marketing events consistent with pancreatitis in vildagliptin agents revealed 42 cases of pancreatitis/acute pancreatitis and 15 cases of reported elevated lipase/amylase. The majority of reported cases had additional risk factors for pancreatitis. A warning statement on acute pancreatitis and that patients should be informed on the characteristic symptoms of acute pancreatitis has been introduced in the product information, in line with the current warnings given for other DPP4-inhibitors. The data provided with this variation is not considered to alter the benefit risk balance for vildagliptin, which remains positive.
IG/0118/G	This was an application for a group of variations.	27/10/2011	n/a		

	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 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 A.7 - Administrative change - Deletion of manufacturing sites 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 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
WS/0170	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To extend the shelf life of the finished product form 24 months to 36 months. B.II.f.1.b.1 - Stability of FP - Extension of the shelf	22/09/2011	12/10/2011	SmPC	

	life of the finished product - As packaged for sale (supported by real time data)				
IG/0089/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	20/07/2011	n/a		
IB/0007	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/07/2011	n/a		
IG/0088/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	11/07/2011	n/a		
WS/0070	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	16/12/2010	24/01/2011	SmPC, Annex II and PL	During the review of the original marketing authorization application for vildagliptin, there was only a limited number of patients > 75 years who had been treated with

	Update of section 4.2 of the SPC following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008, to reflect the safety and efficacy data that the MAH has accumulated in patients > 75 years. The MAH also takes this opportunity to implement the latest QRD template, to update Annex IIB with the new RMP version and to update some local representatives' details 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				vildagliptin (N=113) in clinical studies. Since then, the number of elderly patients ? 75 years treated with vildagliptin has increased. In the enlarged database, 334 patients > 75 years were exposed to vildagliptin, 295 of which are included in the main safety population and up to 187 in the efficacy populations. The majority of the patients were treated with the approved dose 50 mg bid. The submitted analyses support a similar efficacy in elderly patients compared to the younger population with respect to reduction of HbA1c and FPG. The treatment was largely weight neutral and the incidence of hypoglycaemia was low. No other safety issues compared to comparators or the younger population were identified. There are limited safety data on the use of vildagliptin in patients with moderately and severely impaired renal function at risk for higher drug exposure. Until data from ongoing studies in patients with moderate and severe renal impairment become available, the use of vildagliptin is not recommended in this population. This would also apply for the elderly patient population > 75 years.
IG/0032/G	This was an application for a group of variations. To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 9.0, to include: - a change in the deputy of the Qualified Person for Pharmacovigilance (QPPV); - a change in the major contractual arrangements. - administrative changes not impacting the operation of the pharmacovigilance system. Annex II.B has also been updated with the latest	21/12/2010	n/a		

	wording as per October 2010 CHMP procedural announcement. 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.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				
WS/0006/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. This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Section 5.1 of the Summary of Products Characteristics (SPC) has been updated to include information on 2 new vildagliptin studies. Additionally, the adverse event pancreatitis has been added to section 4.8 of the SPC.	20/05/2010	06/07/2010	SmPC, Annex II and PL	The MAH has provided results from two clinical studies (LAF237A2338 and LMF237A2302) and proposed to include information from these studies in section 5.1 of the Summary of Products Characteristics (SPC). The first one was a multicenter, randomized, double-blind, active-controlled study to compare the efficacy and safety of long-term treatment (52 weeks) with vildagliptin to gliclazide in patients with T2DM inadequately controlled with metformin monotherapy. The presented results from this study are in line with what has been seen in previous studies with vildagliptin in combination with sulfonylurea. The second study was a 24-week multicenter, randomized, double-blind, active-controlled initial combination therapy

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data 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				study with the fixed dose combination of vildagliptin plus metformin in drug naïve patients with T2DM. The results of this study demonstrated that initial combination therapy with the fixed dose combination of vildagliptin plus metformin was statistically superior to that of both individual monotherapy components. Initial combination therapy is not recommended as first line treatment in treatment guidelines and is not in line with the approved indication for vildagliptin. However, the CHMP accepted that information on this study was added to section 5.1 of the SPC. A new pooled safety analysis has been performed which integrates data from these new studies and provides an updated assessment of the safety and tolerability of vildagliptin based on data from more than 11,500 patients. The increased database was also utilized to conduct an extensive analysis of the cardiovascular safety of vildagliptin. The CHMP agreed that this information is consistent with the previously submitted pooled safety data and does not signal any new, unidentified concerns. Additionally, section 4.8 of the SPC and relevant section of the Package Leaflet have been updated to include pancreatitis as a post-marketing adverse event.
II/0006	Update of the Detailed Description of the Pharmacovigilance system (DDPS). Changes to QPPV Update of DDPS (Pharmacovigilance)	18/02/2010	26/03/2010	Annex II and PL	With this variation the MAH submitted a new version of the DDPS (core version 8.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements. Consequently, Annex II has been updated with the new version numb er

					of the agreed DDPS. In addition, the Marketing Authorisation Holder took the opportunity to update the local representatives contact details for Finland, Latvia and Luxembourg in the Package Leaflet and to introduce some linguistic changes in the German Annexes.
IA/0005	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	15/12/2009	n/a		
II/0002	Update of SPC Section 4.8 and 5.1 and PL to include information on the results of 3 active-controlled long-term clinical studies. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	21/08/2009	SmPC and PL	During the review of the initial Marketing Authorisation application for vildagliptin, the Marketing Authorisation Holder committed to submit the results of ongoing, active-controlled, long-term, comparative studies. This included one 2-year monotherapy study, one > 2-year add-on combination therapy study with metformin, and one 1-year (24 week + 28 week extension) add-on combination therapy study with metformin. The results of these studies have now become available and are discussed in the current variation application. Furthermore, a review of the safety of vildagliptin has been performed, integrating data from the above studies of up to more than 2 years in duration as well as from additional studies. Concerning efficacy, non-inferiority to the comparators (glimepiride and pioglitazone), according to the pre-specified non-inferiority margins, was achieved in the add-on to metformin studies, but not in the monotherapy study.

					In all studies the absolute reduction of HbA1c with vildagliptin was lower compared to the comparators. Concerning safety, vildagliptin has a hypoglycemia profile superior to that of glimepiride and similar to that of pioglitazone and metformin. Previously, signals concerning hepatic and skin safety have been identified. In the current updated safety data set, slightly higher odds of having a persistent transaminase elevation with vildagliptin were found. Concerning skin safety, the incidences of skin/vascular AEs were low and not statistically significant. No additional safety signals were seen.
N/0003	Update of the list of local representatives in section 6 of the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/08/2009	n/a	PL	
N/0001	Update of the Spanish local representative contact details in section 6 of the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/05/2009	n/a	PL	