Jentadueto

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
II/0070	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to update information on paediatric population based on final results from study DINAMO 1218-0091; this is a double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus. The Package Leaflet is updated accordingly.	22/02/2024		SmPC and PL	Please refer to Scientific Discussion 'Jentadueto-H-C-002279-II-0070' For more information, please refer to the Summary of Product Characteristics.

[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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

	In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0069	A.8 - Administrative change - Changes to date of the audit to verify GMP compliance of the manufacturer of AS	21/08/2023	n/a		
IB/0068	B.II.d.z - Change in control of the Finished Product - Other variation	05/07/2023	n/a		
WS/2377	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 SmPC in order to add a new warning on Vitamin B12 decrease or deficiency and to update the list of adverse drug reactions (ADRs) in accordance with the recent update of the PI for Glucophage, which is the reference label for the compound metformin, and following the request by MHRA on 20 June 2022 for all products containing metformin; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to update the list of local representatives in the Package Leaflet.	02/03/2023		SmPC and PL	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0066/G	This was an application for a group of variations. B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological product) of a specification parameter wit its corresponding test method as a result of a safety or quality issue 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.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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.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.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.a - Change to importer, batch release	23/11/2022	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
IG/1501	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	13/04/2022	n/a		
IAIN/0064/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.7 - Administrative change - Deletion of manufacturing sites	04/03/2022	15/03/2023	Annex II and PL	
PSUSA/10427 /202105	Periodic Safety Update EU Single assessment - linagliptin, linagliptin / metformin	13/01/2022	n/a		PRAC Recommendation - maintenance
IA/0062	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	03/05/2021	n/a		
N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/03/2021	15/03/2023	PL	
IB/0060	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	21/12/2020	n/a		

IA/0059	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)	08/10/2020	n/a		
IA/0058	A.7 - Administrative change - Deletion of manufacturing sites	13/07/2020	n/a		
WS/1835	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	02/07/2020	n/a		
IAIN/0057/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	22/05/2020		SmPC, Labelling and PL	
IG/1221	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate	13/03/2020	n/a		

	from an already approved manufacturer				
WS/1696/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.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.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.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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.z - Change in control of the AS - Other variation	16/01/2020	n/a		

	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.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.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 procedure is already authorised 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.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.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/0054	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/01/2020		PL	
WS/1601	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2 and 5.1 of the Trajenta SmPC, update of sections 4.2, 4.4 and 5.1 of the Jentadueto SmPC and section 5.1 of the Glyxambi SmPC, based on the final results from study 1218.74 (CAROLINA study) listed as a category 3 study in the RMP of Jentadueto and Trajenta, in order to fulfil Trajenta MEA 008.1 and Jentadueto MEA 001.1; this is a phase III randomized, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk. The Package Leaflet for Trajenta is updated accordingly. The RMP version 13.1 for Jentadueto and Trajenta and version 5.1 for Glyxambi have also been submitted. In addition, the Worksharing applicant (WSA) took the opportunity to make corrections throughout the product information for Glyxambi and Jentadueto and to make corrections to the Bulgarian, French, Swedish translations for Glyxambi.	31/10/2019		SmPC and PL	The MAH updated sections 4.2 and 5.1 of the Trajenta SmPC, sections 4.2, 4.4 and 5.1 of the Jentadueto SmPC and section 5.1 of the Glyxambi SmPC, based on the final results from study 1218.74 (CAROLINA study). The double-blind parallel group CAROLINA study evaluated the cardiovascular safety of linagliptin versus glimepiride as adjunct to standard care therapy in patients with type 2 diabetes and with increased CV risk. A total of 6033 patients were treated (linagliptin 5 mg: 3023, glimepiride 1 mg to 4 mg: 3010) and followed for a median of 6.25 years. The mean age was 64 years, the mean HbA1c was 7.15 %, and 60 % were male. Approximately 19 % of the population had an eGFR <60 mL/min/1.73 m2. The study was designed to demonstrate non-inferiority for the primary cardiovascular endpoint which was a composite of the first occurrence of cardiovascular death or a non-fatal myocardial infarction (MI) or a non-fatal stroke (3P-MACE). Linagliptin did not increase the risk of the combined endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke (MACE-3) [Hazard Ratio (HR)=0.98; (95 % CI 0.84, 1.14); p<0.0001 for non-inferiority], when added to standard of care in adult patients with type 2 diabetes with increased CV risk compared to glimepiride.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0052	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/07/2019		SmPC and PL	
IG/1077	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	14/03/2019	n/a		
WS/1461	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 , 4.8 and 5.1 of the SmPC to update the warnings related to acute pancreatitis and bullous pemphigoid and the efficacy and safety information based on final results from study listed as a category 3 in the RMP "A multicenter, international, randomized, parallel group, double blind, placebo-controlled CArdiovascular Safety & Renal Microvascular outcomE study with LINAgliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk (CARMELINA)". The RMP have also been updated accordingly for all products (Trajenta and Jentadueto version 12.1, Glyxambi version 4.1) and to be in accordance with the revision 2 of the RMP template.	14/03/2019	18/07/2019	SmPC	The SmPC sections 4.4, 4.8 and 5.1 have been updated to reflect the results of CARMELINA study on acute pancreatitis and bullous pemphigoid and on the efficacy and safety information of linagliptin. CARMELINA study evaluated the cardiovascular and renal safety of linagliptin 5 mg once daily versus placebo as adjunct to standard care therapy in patients with type 2 diabetes and with increased cardiovascular risk evidenced by a history of established macrovascular or renal disease.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/1469	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		
PSUSA/10427 /201805	Periodic Safety Update EU Single assessment - linagliptin, linagliptin / metformin	29/11/2018	n/a		PRAC Recommendation - maintenance
IG/0991	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	04/10/2018	n/a		
IA/0048/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	04/10/2018	n/a		

IB/0044/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.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 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.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	20/07/2018	18/07/2019	Annex II and PL	
IAIN/0043	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	12/10/2017	n/a		

WS/1201/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.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.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.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	14/09/2017	n/a		
IB/0042/G	This was an application for a group of variations. B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue	15/08/2017	n/a		

	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
WS/1171	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.3.z - 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 - Other variation	22/06/2017	16/03/2018	SmPC and PL	
WS/1162	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/06/2017	16/03/2018	SmPC	
IG/0798/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	05/05/2017	n/a		

	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 A.7 - Administrative change - Deletion of manufacturing sites				
WS/1140	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/03/2017	16/03/2018	SmPC and PL	
R/0036	Renewal of the marketing authorisation.	26/01/2017	22/03/2017	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Jentadueto in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. In addition sections 4.6 'Fertility, pregnancy and lactation' of the SmPC has been updated to align the information on pregnancy with the SmPC guideline and section 4.8 'Undesirable effects' of the SmPC has also been updated to simplify how the safety data is presented for this fixed-dose combination product in line with the SmPC guideline.

WS/0915	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 to include the use of Trajenta and Jentadueto in combination with other diabetes medicines; as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated based on studies 1245.30, 1275.10 and 1275.1. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to make minor editorial changes in the PI. Moreover, the RMP version 10 (for Trajenta) and version 12 (for Jentadueto) have been updated. Furthermore, the PI is brought in line with the latest QRD template version 10.0. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/12/2016	27/01/2017	SmPC and PL	Please refer to the Scientific Discussion for Trajenta /Jentadueto H/C/WS0915.
A31/0029	Pursuant to Article 31 of Regulation (EC) No 726/2004, the European Commission requested on 25 January 2016 the opinion of the European Medicines Agency on the adequacy of the current recommendations for metformin containing products with respect to the use in patients with moderate renal failure, taking into account the available information on the risk of lactic acidosis. The CHMP was requested to assess the impact thereof on the benefit-risk balance of metformin containing	13/10/2016	12/12/2016	SmPC and PL	Please refer to the assessment report: Metformin containing medicinal products - EMEA/H/A-31/1432

	products and to give its recommendation whether the marketing authorisation of this product should be maintained, varied, suspended or revoked. The notification for the procedure is appended to this opinion.				
IA/0035	B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation	14/09/2016	n/a		
IB/0034/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.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 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	11/08/2016	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
IB/0033	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	28/06/2016	n/a		
IA/0032/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.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	08/06/2016	n/a		
II/0031	Update of section 4.8 of the SmPC in order to update ADR frequency categories based on the pooled safety analysis of the placebo-controlled trials undertaken. 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	28/04/2016	12/12/2016	SmPC and PL	Compared with the previous ADR frequency update, 'hypersensitivity' has changed frequency category from 'rare' to 'uncommon' for the linagliptin+metformin combination. The ADR 'diarrhoea' changed frequency category from 'uncommon' to 'common' for the linagliptin+metformin combination. The ADR 'liver function disorders' (for patients in whom linagliptin and metformin were combined with insulin) has changed frequency category from 'common' to 'uncommon'.

PSUSA/9214/ 201505	Periodic Safety Update EU Single assessment - linagliptin / metformin	17/12/2015	02/03/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9214/201505.
WS/0800	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 4.3, 4.4 and 4.5 of the SmPC in order to align the SmPC for Jentadueto and Synjardy to the safety information for the UK metformin label (Glucophage) with regard to tissue hypoxia, lactic acidosis, compromised cardiac or renal function and administration of iodinated contrast agents. In addition, the Worksharing applicant (WSA) took the opportunity to update the list of local representatives for Spain and Portugal in the Package Leaflet for Jentadueto and to bring the PI of Jentadueto in line with the latest QRD template version 9.1. The RMPs (version 3.0 for Synjardy and version 11.0 for Jentadueto) for both products have been updated according to the SmPC changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/10/2015	26/02/2016	SmPC, Annex II and PL	Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure or acute worsening of renal function. Special caution should be paid to situations where renal function may become impaired, for example in case of dehydration (severe diarrhoea or vomiting), or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). In the acute conditions listed, metformin should be temporarily discontinued. The intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure. This may induce metformin accumulation and may increase the risk for lactic acidosis. Therefore, this medicinal product must be discontinued prior to, or at the time of the test and not be reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further. Other associated risk factors should be considered to avoid lactic acidosis such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic impairment and any condition associated with hypoxia (such as decompensated cardiac failure, acute myocardial infarction). Patients with heart failure are more at risk of hypoxia and

					renal insufficiency. In patients with stable chronic heart failure, the combination with metformin may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, the combination is contraindicated due to the metformin component. The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps, digestive disorders as abdominal pain and severe asthenia. Patients should be instructed to notify these signs immediately to their physicians if they occur, notably if patients had a good tolerance to the combination including metformin before. The combination should be discontinued, at least temporarily, until the situation is clarified. Reintroduction of the combination should then be discussed taking into account the benefit/risk ratio in an individual basis as well as renal function. In case of lactic acidosis, the patient should be hospitalised immediately. Physicians should alert the patients on the risk and on the symptoms of lactic acidosis.
II/0026	Submission of a revised RMP in order to add cardiac failure as important potential risk. 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	21/05/2015	n/a		

PSUV/0022	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/11/2014	27/05/2015	PL	
WS/0524	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	25/09/2014	27/05/2015	SmPC and PL	
IA/0024	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	01/09/2014	n/a		
IAIN/0023	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	19/08/2014	n/a		
IA/0021/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	12/08/2014	n/a		

	procedure				
IA/0020/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.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	25/07/2014	n/a		
IB/0018/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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 B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any	08/05/2014	27/05/2015	Annex II and PL	

	manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products 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.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation				
IG/0432	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/04/2014	n/a		
IB/0016	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	18/02/2014	n/a		
PSUV/0014	Periodic Safety Update	06/02/2014	n/a		PRAC Recommendation - maintenance
II/0012	Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to add a new indication for the use of Jentadueto in combination with insulin in adult	18/12/2013	24/01/2014	SmPC and PL	Please refer to Scientific Discussion Jentadueto-H-2279-II-12-en.

	patients with type 2 diabetes when insulin and metformin do not provide adequate glycaemic control. The Package Leaflet was updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0015/G	This was an application for a group of variations. B.II.e.z - Change in container closure system of the Finished Product - Other variation 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.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	27/11/2013	n/a		
IG/0350	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	30/08/2013	24/01/2014	SmPC and PL	
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/08/2013	24/01/2014	PL	

IB/0009	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	02/05/2013	n/a		
IB/0008	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	02/05/2013	n/a		
IAIN/0010	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	12/04/2013	n/a		
WS/0356	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 in order to update the information with the current data from the cardiovascular risk meta-analysis. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/03/2013	22/04/2013	SmPC	In this variation the MAH has provided an update of the prospective CV meta-analysis. A first analysis of this study was submitted with the MAA. Additionally an updated summary was performed in 2011 to support the types II variation for the add-on to insulin indication (EMEA/H/C/002110/II/0004/G). Compared to earlier analyses no significant changes have been observed. In total there were 60 primary events on linagliptin and 62 on comparators. The overall CV risk ratio was not significantly reduced for linagliptin versus combined comparators. No difference in CV risk for linagliptin was observed versus placebo in the placebo-controlled trials only. The secondary and tertiary composite CV endpoints also do not show an increased risk for linagliptin as compared with combined comparators. Section 5.1 of the SmPC has been updated to reflect this new data.
WS/0351	This was an application for a variation following a worksharing procedure according to Article 20 of	21/03/2013	22/04/2013	SmPC, Annex	Following the assessment of the latest PSUR for linagliptin, the CHMP requested that, considering the reported de- and

	Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in order to include the new adverse reaction "rash" following a CHMP request after the evaluation of the latest PSUR. The Package Leaflet was updated accordingly. In addition, the MAH took the opportunity to implement minor typographical corrections in the SmPC. Furthermore, Annex II was updated to reflect the latest version of the QRD template. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH			II and PL	re-challenge cases, "rash" should be clearly included as a new adverse reaction in the product information. The MAH has complied with the mentioned CHMP request. Based on the incidence of "rash" in clinical trials (0.4%), frequency uncommon was proposed to be assigned, and the CHMP considered it to be acceptable. Furthermore, the MAH proposals to: - change of the frequency of "hypersensitivity" from uncommon to rare and - addition of "urticaria" and "angioedema" to the SOC "Skin and subcutaneous tissue disorders" with the frequency rare. For these ADRs an asterix is used to indicate that these events were derived from post-marketing experience; were in line with the conclusions of PSUR-2 and therefore were considered acceptable by the CHMP. The other proposed changes and corrections to the SmPC and PL were accepted. Based on the information presented by the MAH to support this variation, there is no impact on the overall benefit/risk balance.
IB/0007	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	19/03/2013	22/04/2013	SmPC	
IB/0006	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	06/03/2013	n/a		
IB/0003/G	This was an application for a group of variations.	02/10/2012	n/a		

	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				
IB/0002/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g.	21/09/2012	25/10/2012	SmPC, Labelling and PL	

	tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes				
IG/0211	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/09/2012	n/a		