Ristaben

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
WS/2545/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. A.7 - Administrative change - Deletion of	14/09/2023		SmPC, Labelling and PL	

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

	manufacturing sites B.II.c.1.f - Change in the specification parameters and/or limits of an excipient - Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue B.II.c.1.f - Change in the specification parameters and/or limits of an excipient - Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue 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.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale B.I.e.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supportive data				
IA/0076/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of	13/07/2023		Annex II and PL	

	manufacturing sites				
N/0075	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/06/2023		PL	
WS/2390	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.e.2 - Introduction of a post approval change management protocol related to the AS	30/03/2023	n/a		
IG/1568	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	09/11/2022	n/a		
N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/06/2022	29/09/2022	PL	
IG/1514	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	21/06/2022	n/a		
WS/2091	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	16/09/2021	29/09/2022	SmPC, Labelling and PL	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
WS/2082	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	02/09/2021	n/a		
IG/1426	A.7 - Administrative change - Deletion of manufacturing sites	03/08/2021	n/a		
PSUSA/10673 /202008	Periodic Safety Update EU Single assessment - sitagliptin, metformin hydrochloride / sitagliptin	11/03/2021	n/a		PRAC Recommendation - maintenance
IG/1369	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	09/03/2021	n/a		
IG/1351/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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)	11/02/2021	27/08/2021	Annex II and PL	

N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/12/2020	27/08/2021	PL	
IG/1313	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	09/12/2020	n/a		
WS/1803	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/05/2020	27/08/2021	SmPC and PL	
IB/0061	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/03/2020	n/a		
WS/1727	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the SmPC sections 4.2, 4.8, 5.1 and 5.2, to include the data from paediatric study P083 (EMEA-000470-PIP01-08-M11), and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the Annexes in line with the latest QRD template.	30/01/2020	09/03/2020	SmPC, Annex II, Labelling and PL	A 54-week, double-blind study was conducted to evaluate the efficacy and safety of sitagliptin 100 mg once daily in paediatric patients (10 to 17 years of age) with type 2 diabetes who were not on antihyperglycaemic therapy for at least 12 weeks (with HbA1c 6.5% to 10%) or were on a stable dose of insulin for at least 12 weeks (with HbA1c 7% to 10%). Patients were randomised to sitagliptin 100 mg once daily or placebo for 20 weeks. Mean baseline HbA1c was 7.5%. Treatment with sitagliptin 100 mg did not provide significant improvement in HbA1c at 20 weeks. The reduction in HbA1c in patients treated with sitagliptin

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				(N=95) was 0.0% compared to 0.2% in patients treated with placebo (N=95), a difference of -0.2% (95% CI: -0.7, 0.3). The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. This is not considered to be a clinically meaningful difference compared to adult patients based on the flat PK/PD relationship between the dose of 50 mg and 100 mg. No studies with sitagliptin have been performed in paediatric patients with age <10 years. In clinical trials with sitagliptin in paediatric patients with type 2 diabetes mellitus aged 10 to17 years, the profile of adverse reactions was comparable to that observed in adults. Sitagliptin should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Sitagliptin has not been studied in paediatric patients under 10 years of age.
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/03/2019	09/03/2020	Labelling and PL	
IG/1012	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	18/12/2018	n/a		
WS/1357	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	29/11/2018	n/a		

	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				
T/0057	Transfer of Marketing Authorisation	17/07/2018	23/08/2018	SmPC, Labelling and PL	
PSUSA/2711/201708	Periodic Safety Update EU Single assessment - sitagliptin	22/03/2018	22/05/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2711/201708.
IG/0903	A.7 - Administrative change - Deletion of manufacturing sites	05/02/2018	n/a		
IG/0886	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	24/01/2018	n/a		
IG/0874	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	21/12/2017	n/a		
WS/1211	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	09/11/2017	15/12/2017	SmPC, Labelling and PL	For patients with mild renal impairment (glomerular filtration rate [GFR] ☐ 60 to < 90 ml/min), no dose adjustment is required. For patients with moderate renal

	Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to modify the information on dosing, an existing warning and administration instructions, respectively for use of sitagliptin in patients with type 2 diabetes mellitus and renal impairment. Consequently, the RMP version 8 has also been updated accordingly. In addition, the WSA took the opportunity to update the list of local representatives in the Package Leaflet for Tesavel and to bring the Product Information (PI) in line with the latest QRD template version 10. Minor editorial changes are also introduced in the Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				impairment (GFR ☐ 45 to < 60 mL/min), no dosage adjustment is required. For patients with moderate renal impairment (GFR ☐ 30 to < 45 mL/min), the dose of Januvia is 50 mg once daily. For patients with severe renal impairment (GFR ≥ 15 to <30 mL/min) or with end stage renal disease (ESRD) (GFR < 15 mL/min), including those requiring haemodialysis or peritoneal dialysis, the dose of Januvia is 25 mg once daily. Treatment may be administered without regard to the timing of dialysis. A single dose, open label study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50 mg) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment, as well as patients with ESRD on haemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate, or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses. Compared to normal healthy control subjects, plasma AUC of sitagliptin was increased by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment (GFR ≥ 60 to < 90 mL/min) and patients with moderate renal impairment (GFR ≥ 45 to < 60 mL/min), respectively. Plasma AUC of sitagliptin was increased approximately 2 fold in patients with moderate renal impairment (GFR ≥ 30 to < 45 mL/min), and approximately 4 fold in patients with severe renal impairment (GFR < 30 mL/min), including in patients with ESRD on haemodialysis.

WS/1202/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.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	16/11/2017	n/a		
WS/1141	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 of the SmPC in order to add a warning on bullous pemphigoid following the PRAC assessment outcome of EMEA/H/C/PSUSA/2711/201408; the Package Leaflet is being updated accordingly. Consequently, the RMP	09/06/2017	03/10/2017	SmPC and PL	There have been post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including sitagliptin. If bullous pemphigoid is suspected, Januvia should be discontinued.

	is also updated accordingly (finally agreed version 7.1). 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				
WS/1131	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.d.2.z - Change in test procedure for the finished product - Other variation	30/03/2017	n/a		
IG/0782/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.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS	17/03/2017	n/a		
IG/0743	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	30/11/2016	n/a		

IG/0728/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	10/10/2016	03/10/2017	Annex II and PL	
IG/0731/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites 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	22/09/2016	n/a		
IG/0694	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	06/07/2016	n/a		
IG/0659	B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method	11/02/2016	n/a		

WS/0846	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	28/01/2016	30/06/2016	SmPC, Annex II and PL	The TECOS was a randomized study in 14,671 patients in the intention to treat population with an HbA1c of ≥ 6.5 to 8.0 % with established CV disease who received sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m2) or placebo (7,339) added to usual care targeting regional standards for HbA1c and CV risk factors. The study population included 2,004 patients ≥ 75 years of age and 3,324 patients with renal impairment (eGFR= 30-60 mL/min/1.73 m2). Over the course of the study, the overall estimated mean (SD) difference in HbA1c between the sitagliptin and placebo groups was 0.29 % (0.01), 95 % CI (-0.32, -0.27); p < 0.001. After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalization for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo. For more information, please refer to the Summary of Product Characteristics.
IG/0588	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	08/07/2015	n/a		
WS/0741	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	25/06/2015	30/06/2016	SmPC and PL	

	Update of section 4.8 of the SmPC in order to add pruritus as a new ADR with frequency 'uncommon' identified from post marketing experience. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant took the opportunity to make minor correction in section 5.1 of the SmPC and minor editorial changes to the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/2711/ 201408	Periodic Safety Update EU Single assessment - sitagliptin	26/03/2015	28/05/2015	SmPC and PL	Please refer to Januvia PSUSA/00002711/201408 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
WS/0714/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	23/04/2015	n/a		

IG/0519/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.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	26/02/2015	n/a		
IG/0512	A.7 - Administrative change - Deletion of manufacturing sites	09/01/2015	n/a		
R/0033	Renewal of the marketing authorisation.	23/10/2014	16/12/2014	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of Ristaben remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IG/0494	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	07/11/2014	28/05/2015	Annex II and PL	
WS/0534	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	25/09/2014	16/12/2014	SmPC and PL	

	Veterinary Medicinal Products - Other variation				
WS/0558	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 with the results of study MK-0431 PN260 which examined the insulin-sparing effect of sitagliptin 100 mg once-daily compared with placebo over 24 weeks in participants with type 2 diabetes mellitus who have inadequate glycaemic control on insulin alone or in combination with metformin. 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	22/05/2014	19/08/2014	SmPC	A 24 week placebo-controlled study involving 660 patients was designed to evaluate the insulin-sparing efficacy and safety of sitagliptin (100 mg once daily) added to insulin glargine with or without metformin (at least 1,500 mg) during intensification of insulin therapy. Baseline HbA1c was 8.74 % and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. At Week 24, the increase in daily insulin dose was 19 IU/day in patients treated with sitagliptin and 24 IU/day in patients treated with placebo. The reduction in HbA1c in patients treated with sitagliptin and insulin (with or without metformin) was 1.31 % compared to 0.87 % in patients treated with placebo and insulin (with or without metformin), a difference of 0.45 % [95 % CI: -0.60, -0.29]. The incidence of hypoglycaemia was 25.2 % in patients treated with sitagliptin and insulin (with or without metformin) and 36.8 % in patients treated with placebo and insulin (with or without metformin).The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycaemia (9.4 vs 19.2%). There was no difference in the incidence of severe hypoglycaemia.
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/05/2014	19/08/2014	PL	
IG/0413/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished	17/03/2014	19/08/2014	SmPC, Labelling and	

	product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. 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			PL	

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WS/0371/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 introduce 2 new manufacturing sites for the production of sitagliptin active substance and a synthetic intermediate. 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	21/11/2013	n/a		
WS/0370	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To introduce a new manufacturing route for production of sitagliptin active substance. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	21/11/2013	n/a		
IG/0366	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV	08/11/2013	n/a		

	(including contact details) and/or changes in the PSMF location				
IG/0339/G	This was an application for a group of variations. B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	14/08/2013	19/08/2014	Annex II and PL	
WS/0410/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. Grouped worksharing application of a type IB and four type IA: - To add an alternate drug product manufacturing site - To introduce minor changes to the approved manufacturing process at a drug product manufacturing site - To add an alternate batch control/testing site - To add two importation testing sites 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	25/07/2013	n/a		

	packaging, for non-sterile medicinal products B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions 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.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.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				
WS/0329	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 4.8 and 5.1 of the SmPC in order to include results from study P128 (sitagliptin in combination with pioglitazone and metformin) and to remove the information relating to the combination of sitaglitptin and rosiglitazone. The Package Leaflet is updated accordingly. The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet.	15/11/2012	18/12/2012	SmPC and PL	Study P128 was a Phase III, multicentre, randomised double-blind placebo controlled study that evaluated the safety and efficacy of sitagliptin in patients with T2DM and inadequate glycaemic control on combination therapy with metformin and pioglitazone. The study showed that for patients with inadequate glycaemic control on dual combination therapy with metformin and pioglitazone, the addition of sitagliptin 100 mg provided a statistically significant lowering in HbA1c, compared to placebo at Week 26: difference in mean change -0.75 (95% CI -0.95, -0.54) (FAS/LOCF). Analyses of change from baseline in HbA1c for Completers only were in line with the analysis of the FAS/LOCF (-0.60 [-0.80; -

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				0.39]). With respect to fasting plasma glucose, the addition of sitagliptin was statistically significantly greater to the addition of placebo in lowering FPG at Week 26 (sitagliptin -21.6 mg/dL vs. placebo -1.5. mg/dL; difference -20.3 [CI-27.0, -13.6]). The profile over time for this group showed a reduction in FPG levels within the first 6 weeks of treatment with sitagliptin; and generally stable FPG was observed over the remaining double blind treatment period with only a minor trend towards baseline between Weeks 12-26. Body weight was increased in both treatment groups: 1.3 kg in the sitagliptin group vs. 1.1 kg in the placebo group. The difference was not statistically significant. In this 26-week, there was a numerically higher incidence of adverse events in patients treated with sitagliptin in combination with pioglitazone and metformin; however, the 95% CI for the between-group difference included 0. The incidences of drug-related adverse events and serious adverse events were numerically lower in the sitagliptin group relative to the placebo. In addition, the proportion of patients who discontinued from study drug due to adverse events was numerically lower in the sitagliptin group relative to the placebo group. Some specific adverse events occurred at a slightly higher incidence in the sitagliptin group relative to the placebo group. The adverse events were generally mild to moderate in intensity and did not lead to discontinuation of study drug. There was a low incidence of hypoglycaemia with no statistically significant or clinically meaningful differences between groups; this is reflected in section 5.1 of the SmPC. The few events reported in the sitagliptin group were mild, none required assistance for treatment, and

					none caused interruption or discontinuation of study drug. Numerically lower incidences of peripheral oedema were reported in the sitagliptin group than in the placebo group. The table of ADRs in section 4.8 of the SmPC has been updated to reflect the results of study P128. The adverse drug reactions associated with the combination of sitagliptin and rosiglitazone which were previously included in the SmPC have been deleted. Section 5.1 of the SmPC has also been updated to reflect the results of study P128, and results of the study of sitagliptin in combination with rosiglitazone have been deleted.
IG/0230	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	06/11/2012	n/a		
WS/0281	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 section 4.8 of the SmPC to add the adverse drug reaction (ADR) "back pain" with a frequency of “not known”. Section 4.8 was also updated to include the ADR “pain in extremity” for all sitagliptin combinations with a frequency of “not known”. The Package Leaflet was updated accordingly. The WSA also proposed a minor editorial changes to section 5.1 of the SmPC and rectified an error in section 4 of Package Leaflet deleting the text "weight	19/07/2012	30/08/2012	SmPC and PL	The MAH received 91 postmarketing reports of “back pain”, in patients treated with sitagliptin (80 reports) or sitagliptin/metformin FDC (11 reports). The majority of these adverse events of back pain were non-serious. Based on the accumulation of reports of back pain, including 18 serious reports, 42 positive dechalleges and 7 positive rechallenges, an association between back pain and use of sitagliptin and sitagliptin/metformin FDC cannot be excluded. In 42 cases the time to onset was reported, and in 28 (67%) of these cases time to onset (TTO) was <30 days. The MAH received 156 postmarketing reports of “pain in extremity”, in patients treated with sitagliptin (125 reports) or sitagliptin/metformin FDC (31 reports). The majority of

	loss, loss of appetite" to ensure consistency with the SmPC. 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				these adverse events of pain in extremity were non-serious in nature. Based on the accumulated reports of pain in extremity, including 33 serious reports, and 11 positive rechallenges, an association between pain in extremity and use of sitagliptin and sitagliptin/metformin FDC cannot be excluded. In view of the above the CHMP agreed to the update of section section 4.8 of the SmPC to add the adverse drug reaction (ADR) "back pain" with a frequency of "not known". Section 4.8 was also updated to include the ADR "pain in extremity" for all sitagliptin combinations with a frequency of "not known".
IG/0182	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/08/2012	n/a		
WS/0267/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 site responsible for the manufacture and control of the active substance and to reduce the loading of one starting material. 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.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	21/06/2012	21/06/2012		

	Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
WS/0234	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To add a test procedure for the active substance. 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	19/04/2012	19/04/2012		
IB/0018	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	30/03/2012	30/08/2012	SmPC, Annex II, Labelling and PL	
WS/0179	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, 4.4, 5.1 and 5.2 of the SmPC in order to remove the restrictions on the use of sitagliptin in patients with moderate to severe renal insufficiency or end stage renal disease (ESRD) on dialysis. The Package Leaflet is updated in accordance. C.I.4 - Variations related to significant modifications	17/11/2011	22/12/2011	SmPC and PL	The initial marketing authorisation was for use of sitagliptin for the treatment of patients with T2DM and normal or mildly impaired renal function (creatinine clearance ≥50 ml/min). At that time the CHMP considered the clinical experience with sitagliptin in patients with T2DM and moderate or severe renal impairment (creatinine clearance <50 ml/min) to be too limited and the use of sitagliptin in these patients was therefore not recommended. There were in particular, concerns about the cardiovascular safety in these patients, as in study P028 (a study in renally impaired patients) more patients died in the sitagliptin group compared to the placebo/glipizide group (5 vs. 1).

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				The difference was higher than expected on the basis of the randomisation ratio. In the sitagliptin group, 4 of the 5 patients died due to cardiac adverse experiences, while there was no cardiac death in the glipizide group. As a result of this the MAH agreed to a post approval commitment to further assess the efficacy and safety of sitagliptin in these patients in a study of at least 24 weeks duration. In support of the application two studies were submitted, one (P063) in patients with moderate to severe renal impairment (eGFR < 30 mL/min/1.73 m2), and one study in patients with ESRD on dialysis (study P073). Treatment naive patients, patients on a single oral AHA or on low dose dual combination treatment could participate in the study. Patients were randomised to receive sitagliptin or glipizide. Study duration was 54 weeks. The doses of sitagliptin used in the two new studies supporting this Type 2 variation were 50 mg q.d. for patients with moderate renal insufficiency and 25 mg q.d. for patients with severe renal insufficiency or ESRD on dialysis. In both studies a clinically relevant reduction in HbA1c was seen after 54 weeks of treatment, both in the sitagliptin group (-0.76 and -0.72 in study P063 and P073 respectively) and the glipizide group (-0.62 and -0.87, respectively). The criteria for non-inferiority were met in study P063. Secondary endpoints were in line with these results. In general sitagliptin was well tolerated, and the incidences of adverse events were not meaningfully different between treatment groups. There was a difference in the Metabolism and Nutrition

					disorders SOC and Investigations SOC, but the difference was in favour of sitagliptin. Differences were primarily due to a higher incidence of hypoglycaemia or blood glucose decreased in the glipizide group. Incidences of cardiovascular serious adverse events were generally similar in both treatment groups in both populations (moderate to severe renal impairment, and ESRD). In addition, a second analysis, including serious and non-serious events, did not reveal differences between treatment groups. Renal function was not affected by sitagliptin, and laboratory measurements and vital signs did not show meaningful changes or differences. There was a higher incidence of adverse experiences in the Neoplasms Benign, Malignant, and Unspecified (incl. cysts and polyps) SOC, with 8 cases in the sitagliptin group and none in the glipizide group. All cases occurred in the first six months of therapy and represent different type of tumours, making a causal relationship unlikely. The overall incidence of hypoglycaemia was lower in the sitagliptin group compared to the glipizide group. Although a finger stick was not required, a value was reported for most (92-94%) of the patients with adverse events of symptomatic hypoglycaemia. This does not necessarily mean that there was a value for every event. However, in nearly all cases the blood glucose value was below 3.9 mmol/L (70 mg/dL). The conclusion of the assessment is that the benefit/risk for treatment of patients with renal impairment is positive.
IG/0112	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s)	11/10/2011	n/a		

	to the DDPS that does not impact on the operation of the pharmacovigilance system				
WS/0160	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Addition of a manufacturing site. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	22/09/2011	22/09/2011		
WS/0159/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 site and minor changes in the manufacturing process. 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 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.3.a - Change in the manufacturing process of	22/09/2011	22/09/2011		

	the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions				
WS/0129	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This type II variation was submitted following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Further to a CHMP request based on the assessment of PSUR 4 for Janumet and PSUR 7-8 of Januvia, the Product Information (Summary of Product Characteristics section 4.8 and Package Leaflet section 4) is updated by adding arthralgia and myalgia as adverse drug reactions. Furthermore section 4.8 is re-structured in order to improve readability. In addition, MAH took opportunity to update Annex IIB "Other conditions" with the latest wording as per October 2010 CHMP announcement regarding the Pharmacovigilance system and to update section 6 of the Package Leaflet with local representatives for Sweden and The Netherlands. 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	21/07/2011	24/08/2011	SmPC, Annex II and PL	During review period of PSUR 4 for Janumet and PSUR 7-8 of Januvia the MAH reported number of cases of positive de- and rechallenges that were indicative of a causal relation for arthralgia and myalgia. Following the review of the PSUR 7-8 the CHMP requested to include arthralgia and myalgia as adverse drug reactions reported during post-marketing period. Subsequently MAH applied to update Product Information (Summary of Product Characteristics section 4.8 and Package Leaflet section 4) by adding arthralgia and myalgia as adverse drug reactions. Furthermore, following the CHMP request, MAH applied to re-structure section 4.8 and present the adverse reactions identified from clinical studies and from post-marketing experience in one table with reduced footnotes in order to present clearer safety information. In addition, MAH took opportunity to update Annex IIB "Other conditions" with the latest wording as per October 2010 CHMP announcement regarding the Pharmacovigilance system and to update section 6 of the Package Leaflet with local representatives for Sweden and The Netherlands.

	MAH				
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/07/2011	n/a	PL	
WS/0138/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.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.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	23/06/2011	23/06/2011		
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/05/2011	n/a	PL	

IG/0042	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	31/01/2011	n/a		
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/12/2010	n/a	PL	
WS/0046	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics and Package Leaflet 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	21/10/2010	26/11/2010	SmPC, Annex II and PL	This type II variation concerned an update of section 4.4 and 4.8 of the SmPC to add a warning regarding pancreatitis. The Package Leaflet has been updated accordingly. The variation is consequential to the review of a PSUR and subsequent PhVWP discussion during which the MAH was requested to perform a thorough analysis of the relation between sitagliptin and pancreatitis, incorporating all relevant preclinical, clinical and post-marketing data. The review of this data revealed the need to further strengthen the wording in the product information regarding this topic. In addition, the MAH took the opportunity to make some editorial changes to the annexes in line with the latest QRD template (version 7.3). This application was submitted for a Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.
IG/0027/G	This was an application for a group of variations. C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s)	10/11/2010	n/a	Annex II	

	to the DDPS that does not impact on the operation of the pharmacovigilance system				
WS/0025	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The variation concerns an update of section 4.8 of the SPC to add the adverse reaction "vomiting". Section 4 of the Package Leaflet has been updated accordingly. In addition the MAH has reviewed section 5.1 of the SPC to make a minor correction to the efficacy data from the active-controlled study with metformin (P049). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/09/2010	03/11/2010	SmPC and PL	This type II variation was submitted following a work sharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The variation concerns an update of section 4.8 of the SPC to add the adverse reaction "vomiting". Section 4 of the Package Leaflet has been updated accordingly. In addition the MAH has reviewed section 5.1 of the SPC to make a minor correction to the efficacy data from the active-controlled study with metformin (P049).
WS/0009	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The variation concerns an update of section 4.8 of the SPC to add the adverse reaction impaired renal function including acute renal failure under post-marketing data. Section 4 of the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make editorial changes and to update the SPC and Package Leaflet in line with the latest QRD template (version 7.3).	24/06/2010	06/08/2010	SmPC and PL	

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IG/0016	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	04/08/2010	n/a		
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/07/2010	n/a	PL	