EMA/311095/2020

Janumet

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/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		SmPC and PL	

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

N/0092	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/04/2019		Labelling and PL	
WS/1357	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.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	29/11/2018	n/a		
T/0090	Transfer of Marketing Authorisation	23/05/2018	29/06/2018	SmPC, Labelling and PL	
IG/0933	A.7 - Administrative change - Deletion of manufacturing sites	29/05/2018	n/a		
PSUSA/2003/ 201708	Periodic Safety Update EU Single assessment - metformin hydrochloride / 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/2003/201708.
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/1212/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. Update of sections 4.2 and 5.2 of the SmPC in order to modify the information on dosing, and administration instructions respectively for use of sitagliptin/metformin in patients with type 2 diabetes mellitus and moderate renal impairment. Consequently, the RMP version 8 has also been updated accordingly. Section 4.5 of the SmPC is also updated to extend the existing warning on the concomitant use of metformin with cimetidine to other medicines potentially interfering the renal excretion of metformin, such as ranolazine, vandetanib and dolutegravir. In addition, the Worksharing applicant (WSA) took the opportunity to update the list of local representatives in the Package Leaflet for Efficib and to bring the Product Information (PI) in line with the latest QRD template version 10. Minor editorial changes are also introduced in the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to	09/11/2017	15/12/2017	SmPC, Labelling and PL	For patients with moderate renal impairment and a GFR of 45-49 mL/min, the maximum sitagliptin daily dose of 100 mg can be used. For detailed posology recommendations please refer to the Summary of Product Characteristics. 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. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary. AUC of sitagliptin was increased approximately 2 foldin 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 patients with ESRD on haemodialysis. Concomitant use of drugs that interfere with common renal

	new quality, preclinical, clinical or pharmacovigilance data				tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use. Close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when such products are co administered.
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/1130/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. C.I.11.b: Submission of an updated RMP in order to add a targeted questionnaire related to lactic acidosis as part of the outcome of the referral procedure EMEA/H/A-31/1432 (finally agreed version 7.1). C.I.3.b: 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. 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 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	09/06/2017	15/12/2017	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, Janumet should be discontinued.
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	17/03/2017	n/a		

	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				
IG/0760	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	07/02/2017	n/a		
A31/0077	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 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.	13/10/2016	12/12/2016	SmPC and PL	Please refer to the assessment report: Metformin containing medicinal products - EMEA/H/A-31/1432
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	30/11/2016	n/a		

	pharmaceutical group as the currently approved manufacturer				
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		
PSUSA/2003/ 201508	Periodic Safety Update EU Single assessment - metformin hydrochloride / sitagliptin	17/03/2016	n/a		PRAC Recommendation - maintenance
WS/0830	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	25/02/2016	n/a		
WS/0847	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	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

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				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/0655	A.7 - Administrative change - Deletion of manufacturing sites	07/01/2016	n/a		
IG/0628/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	16/11/2015	n/a		
IG/0626	B.II.b.3.a - Change in the manufacturing process of	12/11/2015	n/a		

	the finished or intermediate product - Minor change in the manufacturing process				
IG/0609	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)	25/08/2015	n/a		
IG/0596/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 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	19/08/2015	30/06/2016	Annex II and PL	
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/0742	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 (frequency uncommon) as a new adverse reaction identified from post marketing experience. In addition, "bullous pemphigoid" and "arthopathy" as adverse reactions (frequency 'unknown) were also added to section 4.8 as a result of PSUR assessment (PSUR procedure EMEA/H/C/PSUSA/00002711/201408). The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor correction in section 5.1 and section 5.2 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				
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/0533	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	19/03/2015	n/a		
IB/0065	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/03/2015	13/05/2015	SmPC, Annex II, Labelling and PL	
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/0513/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	09/01/2015	n/a		
WS/0653/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.	20/11/2014	n/a		

	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.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				
IG/0489	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	30/10/2014	n/a		
WS/0535	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 and update of the RMP, upon request by the CHMP, to implement the CHMP recommendations of the Art. 5(3) referral procedure regarding GLP-1-based therapies and pancreatic safety. The Package Leaflet was updated accordingly. Further, the RMP was updated to include rhabdomyolisis as a potential risk as an outcome of post-authorisation measure LEG 006.2. The MAH also	25/09/2014	13/05/2015	SmPC, Annex II, Labelling and PL	The warning in section 4.4 of the SmPC has been strengthened as follows: Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, Janumet and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is

	took the opportunity to implement editorial changes to the labelling and Package Leaflet, and to implement the latest QRD template, version 9.0. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				confirmed Janumet should not be restarted. Caution should be exercised in patients with a history of pancreatitis.
WS/0559	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	13/05/2015	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: -0.62, -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.
IG/0414/G	This was an application for a group of variations.	17/03/2014	03/06/2014	SmPC,	

	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 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			Labelling and PL	

	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 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				
WS/0469	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Minor change in the manufacturing process of the finished product B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	23/01/2014	n/a		
WS/0390/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/0386	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	21/11/2013	n/a		

	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				
IG/0366	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	08/11/2013	n/a		
IG/0346/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	03/09/2013	n/a		
N/0053	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/08/2013	03/06/2014	PL	
IG/0308/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	24/05/2013	03/06/2014	SmPC, Labelling and PL	

	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				
IG/0282	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	24/05/2013	03/06/2014	SmPC, Labelling and PL	
R/0047	Renewal of the marketing authorisation.	17/01/2013	13/03/2013	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP was of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Janumet continues to be favourable. The CHMP recommended the renewal of the Marketing Authorisation for Janumet, subject to the conditions as laid down in Annex II to the Opinion. The CHMP was also of the opinion that the renewal can be granted with unlimited validity. The renewal required amendments to the terms of the

					Community Marketing Authorisation in order to align the product information with the current QRD template version 8.2.
IG/0250	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	07/12/2012	n/a		
WS/0328	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. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	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; -0.39]). With regards 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/0284	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Addition of an alternate Metformin Hydrochloride active substance manufacturer B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions	20/09/2012	20/09/2012		
WS/0270/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. Update of: • Section 4.8 of the SmPC to include safety information related to "interstitial lung disease", as requested in the Januvia Renewal EMEA/H/C/0722/R/014 (CD 23/02/2012); • Section 4.8 of the SmPC to add safety information related to "back pain" and "pain in	19/07/2012	23/08/2012	SmPC, Annex II, Labelling and PL	The MAH has 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. Therefore, the CHMP agreed that this event should be added to section 4.8 of the SmPC for both sitagliptin and

	extremity", and • Section 5.2 of the SmPC in order to delete information regarding renal impairment to allign the PI with sitagliptin PI as per variation EMEA/H/C/0722/WS/0179 (CD 22/12/2011). The Package Leaflet was updated accordingly. The applicant has taken the opportunity to rectify an error in section 4 of Package Leaflet deleting the text "weight 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. Furthermore, the PI is being brought in line with the latest QRD template version 8.1. 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.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				sitagliptin/metformin fixed-dose combination (FDC) as a postmarketing adverse event. The MAH has received 156 postmarketing reports of "pain in extremity", in patients treated with sitagliptin (125 reports) or sitagliptin/metformin FDC (31 reports). The majority of 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. Therefore, the CHMP agreed that this event should be added to section 4.8 of the SmPC for both sitagliptin and sitagliptin/metformin fixed-dose combination (FDC) as a postmarketing adverse event. The term "interstitial lung disease" was added to the table in section 4.8 of the SmPC, with frequency assigned as "not known" for all dosing regimens represented in the table. This term was added for consistency with the current SmPC for sitagliptin. Interstitial lung disease was added to the SmPC for sitagliptin during the five-year renewal procedure. The statement "Sitagliptin is not recommended for use in patients with moderate to severe renal impairment including those with ESRD since experience in these patients is too limited (see section 4.2)." was deleted from section 5.2 of the SmPC. This deletion is proposed for consistency with the current SmPC for sitagliptin. The corresponding text was deleted from the SmPC for sitagliptin during variation WS-0179, which resulted in approval for use of lower doses of sitagliptin in patients with moderate or severe renal impairment or End Stage Renal Disease (ESRD).

					Other revisions made to sections 4.2, 4,4 and 5.1 of the SmPC for sitagliptin during WS-0179 do not apply to sitagliptin/metformin FDC, because the FDC remains contraindicated in patients with moderate or severe renal impairment as the use of metformin is contraindicated in patients with these disorders. Therefore only section 5.2 has been revised in the SmPC for FDC. This was accepted by the CHMP.
IG/0182	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/08/2012	n/a		
WS/0268/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 - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	21/06/2012	21/06/2012		

WS/0235	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		
N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/12/2011	23/08/2012	PL	
IB/0018/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.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 the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions	15/11/2011	n/a		

IG/0112	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	11/10/2011	n/a		
IG/0120	B.II.a.3.b.1 - Changes in the composition (excipients) of the finished product - Other excipients - Any minor adjustment of the quantitative composition of the finished product with respect to excipients	05/10/2011	n/a		
WS/0156	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/0130	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	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

	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 MAH				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.
WS/0137/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	23/06/2011	23/06/2011		

	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				
N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/05/2011	n/a	PL	
WS/0126/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.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.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	19/05/2011	19/05/2011		
IG/0046	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	11/02/2011	n/a		

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/0016	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/0026	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. 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"; this update is based on postmarketing reports of vomiting received by the MAH. Section 4 of the Package Leaflet has been updated accordingly.
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). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/06/2010	06/08/2010	SmPC and PL	

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		
IG/0008	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	09/06/2010	n/a		
IG/0003	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	06/05/2010	n/a	Annex II and PL	
IG/0002	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	06/05/2010	n/a		
II/0013	Extension of indication for the treatment of Janumet as add on to insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dosage of insulin and metformin alone do not provide adequate glycaemic control. Also Annex II has been updated to reflect the new version number of the Risk Management Plan (RMP). Extension of Indication	24/09/2009	28/10/2009	SmPC, Annex II and PL	Refer to the Scientific Discussion: Janumet-H-861-II-13-AR.

IB/0014	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	20/10/2009	n/a		
IA/0015	IA_32_a_Change in batch size of the finished product - up to 10-fold	08/10/2009	n/a		
II/0012	Update of Summary of Product Characteristics and Package Leaflet to include the side effects pancreatitis and cutaneous vasculitis. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	16/09/2009	SmPC and PL	The MAH has provided a cumulative review of cases reporting pancreatitis and cutaneous vasculitus while on sitagliptin therapy. In clinical trials the number of pancreatitis cases is very low. However, since market introduction, 108 cases of (acute) pancreatitis were reported. For 38 of the cases, the lack of information did not allow full assessment. Two fatalities were reported, but the cases are confounded by several serious co-morbidities and concomitantly used medication. Based on the provided data, a causal relation between the use of sitagliptin and the occurrence of pancreatitis cannot be ruled out. Therefore, the inclusion of pancreatitis to section 4.8 of the Summary of Product Characteristics (SPC) is acceptable. A total of 15 cases of cutaneous vasculitis were reported spontaneously and in clinical trials. In the majority of these cases, patients were suffering from multiple co-morbidities and using many drugs concomitantly. Taking into account the fact that hypersensitivity reactions are known for sitagliptin-containing products (labeled in the current SPC) and the positive de- and rechallenge in an extensively documented case report, a causal relation between the use of sitagliptin and the occurrence of vasculitis is considered to be likely. The addition of cutaneous vasculitis to section

					4.8 is therefore acceptable.
II/0011	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Annex II has been updated to reflect the version number of the DDPS. The MAH also took the opportunity to update the details of the local representatives in the Package Leaflet. Update of DDPS (Pharmacovigilance)	25/06/2009	29/07/2009	Annex II and PL	The MAH updated its DDPS and submitted therefore this type II variation. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements and is considered acceptable.
II/0003	Extension of indication to include use in combination with a PPAR agonist and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control. In addition, few minor changes have been added to Section 5.1 of the SPC to describe the effects of sitagliptin and metformin on GLP-1 concentrations and section 4.9 of the SPC to include data from a Phase-I multiple dose study. Extension of Indication	23/04/2009	02/06/2009	SmPC and PL	Refer to the Scientific Discussion: Janumet-H-861-II-03-AR.
IB/0009	IB_33_Minor change in the manufacture of the finished product	26/03/2009	n/a		
IB/0008	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	26/03/2009	n/a		
IA/0010	IA_32_a_Change in batch size of the finished product - up to 10-fold	25/02/2009	n/a		

IA/0005	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	10/12/2008	10/12/2008	SmPC, Labelling and PL	
IA/0004	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	10/12/2008	10/12/2008	SmPC, Labelling and PL	
IA/0002	IA_05_Change in the name and/or address of a manufacturer of the finished product	02/09/2008	n/a		