Onglyza

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0057	Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to include safety, efficacy and pharmacokinetic information in paediatric patients with Type 2 diabetes mellitus (T2DM) aged 10 to <18 years of age based on interim results from study D1680C00019 (T2NOW). This is a 26-week,	29/02/2024	19/04/2024	SmPC and PL	Onglyza has not been studied in children under 10 years of age. The efficacy of Onglyza in children aged 10 to <18 years has not been established. Therefore, treatment of children and adolescents with saxagliptin is not recommended. In a paediatric study, patients aged 10 to <18 years old

[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).

	multicentre, randomised, placebo-controlled, double-blind, parallel group, Phase III trial with a 26-week safety extension period evaluating the safety and efficacy of dapagliflozin (5 and 10 mg), and separately, saxagliptin (2.5 and 5 mg) in paediatric patients with T2DM who were between 10 and below 18 years of age. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity bring the PI in line with the latest QRD template, to introduce editorial changes and to update the contact details of the local representative in the Netherlands in the Package Leaflet. The RMP version 17.1 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				with inadequately controlled type 2 diabetes mellitus were randomised to saxagliptin (88 patients) or placebo (76 patients) as add-on to metformin, insulin or a combination of metformin and insulin. In this 26-week, placebo-controlled, double-blind randomised clinical study with a 26 week safety extension, patients received 2.5 mg saxagliptin (with potential dose-increase to 5 mg) or placebo once daily following a lead-in period. The primary efficacy endpoint was the change in HbA1c from baseline to 26 weeks of treatment. The treatment difference from placebo was not statistically significant [0.44% (95% CI: 0.93, 0.05)]. The safety profile was similar to that observed in the adult population treated with saxagliptin. The pharmacokinetics of saxagliptin and its major metabolite in paediatric patients aged 10 to <18 years with type 2 diabetes mellitus were similar to that observed in adults with type 2 diabetes mellitus. For more information, please refer to the Summary of Product Characteristics.
PSUSA/2685/ 202307	Periodic Safety Update EU Single assessment - saxagliptin, metformin / saxagliptin	07/03/2024	n/a		PRAC Recommendation - maintenance
IG/1624	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	30/10/2023	n/a		
IAIN/0056	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	19/04/2023	19/04/2024	Annex II and PL	

N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/12/2022	19/04/2024	PL	
IA/0054	A.7 - Administrative change - Deletion of manufacturing sites	02/12/2021	13/04/2022	Annex II and PL	
WS/2098	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from study D1680C00016 (MEASURE HF) (listed as a category 3 study in the RMP). This is a 24-week, multicentre, randomised, double-blind, parallel group, placebo-controlled study to investigate the effects of saxagliptin and sitagliptin on cardiac dimensions and function in patients with Type 2 Diabetes Mellitus and Heart Failure. The updated combined RMP version 16 for Komboglyze and Onglyza was agreed during the procedure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	02/12/2021	n/a		n/a
PSUSA/2685/ 202007	Periodic Safety Update EU Single assessment - saxagliptin, metformin / saxagliptin	11/03/2021	n/a		PRAC Recommendation - maintenance
IG/1358/G	This was an application for a group of variations.	03/03/2021	13/04/2022	Annex II and PL	

	A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
WS/1975	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	14/01/2021	n/a		
WS/1743	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 in order to add a new warning about Bullous pemphigoid and section 4.8 of the SmPC to include Bullous pemphigoid as a new ADR with a frequency of 'Not known'. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/03/2020	09/03/2021	SmPC and PL	Based on all available data (literature publications, postmarketing cases and biological plausibility) there is a probable causal relationship between the use of saxagliptin-containing products and Bullous pemphigoid.
II/0048	C.I.11.b - Introduction of, or change(s) to, the	14/02/2019	n/a		

	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				
WS/1289	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 and 5.2 of the SmPC in order to reflect the new saxagliptin renal cut-off value based on post hoc analysis of pooled data from 9 saxagliptin clinical trials. In addition, the Worksharing applicant combined the SmPCs of different strengths, for both Onglyza and Komboglyze. Furthermore, the Worksharing applicant took the opportunity to include required information on two excipients, sodium and lactose, in sections 2 and 4.4 of the SmPC for Onglyza. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/06/2018	02/08/2018	SmPC and PL	No dose adjustment is recommended for patients with mild renal impairment or in patients with moderate renal impairment that have GFR ≥ 45 mL/min. The dose should be reduced to 2.5 mg once daily in patients with moderate renal impairment that have GFR < 45 mL/min and in patients with severe renal impairment.
IG/0934	A.7 - Administrative change - Deletion of manufacturing sites	15/06/2018	n/a		
PSUSA/2685/ 201707	Periodic Safety Update EU Single assessment - saxagliptin, metformin / saxagliptin	08/03/2018	n/a		PRAC Recommendation - maintenance

IG/0892	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	28/02/2018	n/a		
IB/0043/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.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.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters	02/02/2018	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				

	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.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				
IG/0862	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	24/10/2017	n/a		
WS/1078	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	18/05/2017	26/06/2017	SmPC, Labelling and PL	
WS/0960/G	This was an application for a group of variations	18/05/2017	n/a		Based on the review of five epidemiological studies

	following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Group of variations consisting of final epidemiological results for 1) D1680R00011 study related to risk of infection), 2) D1680R00012 study related to risk of severe hypersensitivity,3) D1680R00013 study related to risk for acute kidney injury, 4) D1680R00014 study related to acute liver failure, 5) D1680R00015 study related to major cardiovascular events and 6) update of the RMP to reflect the submission of the 5 epidemiological studies. As a consequence, the RMP (Onglyza: version 12, Komboglyze: version 13) is updated accordingly. In addition, routine changes are made in parts III (pharmacovigilance plan, overview of planned pharmacovigilance actions) and IV. A safety review based on literature has also been included to investigate acute kidney injury associated with saxagliptin/saxagliptin and metformin at the PRAC request. The requested grouped worksharing procedure proposed amendments to the Risk Management Plan (RMP). 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				evaluating each risk and literature data for acute kidney injury, no increased risk for hospitalisation for infection, for severe hypersensitivity events, for acute kidney injury, for acute liver failure, for major cardiovascular events was observed, when initiating treatment with saxagliptin. The submitted RMPs were approved (Onglyza : version 12, Komboglyze : version 13).

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0039/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or	07/07/2016	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
WS/0902	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, upon request by the CHMP following the assessment of the post-authorisation measures LEG 038.1 (Onglyza) and LEG 015.1 (Komboglyze), with information regarding effect on all-cause mortality. In addition, the MAH took the opportunity to implement minor editorial changes in the Package Leaflet and to update the contact information for the local representative in Poland in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/04/2016	11/04/2017	SmPC and PL	In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction (SAVOR) Study, no benefit was observed for MACE or all-cause mortality. The secondary endpoint, all-cause mortality, occurred at a rate of 5.1% in the saxagliptin group and 4.6% in the placebo group. CV deaths were balanced across the treatment groups. There was a numerical imbalance in non-CV death, with more events on saxagliptin (1.8%) than placebo (1.4%) [HR = 1.27; (95% CI 1.00, 1.62); P = 0.051].
WS/0897	This was an application for a variation following a worksharing procedure according to Article 20 of	01/04/2016	n/a		

	Commission Regulation (EC) No 1234/2008. Submission of a final clinical study report for an epidemiological study CV181-102 with the aim to assess risk factors associated with low lymphocyte count in patients with T2DM (PASS study category 3 currently in the RMP) together with an updated RMP v.10. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
WS/0839	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/12/2015	n/a		
IG/0633	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	09/12/2015	n/a		
WS/0851/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.	19/11/2015	n/a		

	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
WS/0810/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.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 new quality, preclinical, clinical or pharmacovigilance data	01/10/2015	10/03/2016	SmPC, Labelling and PL	
IG/0601	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	09/09/2015	n/a		

	(excluding manufacturer for batch release)				
IAIN/0031/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	08/06/2015	n/a		
PSUSA/2685/ 201407	Periodic Safety Update EU Single assessment - saxagliptin, metformin / saxagliptin	26/02/2015	24/04/2015	SmPC and PL	Please refer to Oglyza PSUSA/00002685/201407 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation

IAIN/0030/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing 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	16/03/2015	10/03/2016	Annex II and PL	
IG/0522	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	12/03/2015	n/a		
IA/0028	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	09/12/2014	n/a		
T/0026	Transfer of Marketing Authorisation	23/09/2014	15/10/2014	SmPC, Labelling and PL	Transfer of Marketing Authorisation from Bristol-Myers Squibb/AstraZeneca EEIG to AstraZeneca AB.
WS/0529/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, 4.4, 4.5, 4.8 and 5.1 of the	24/07/2014	15/10/2014	SmPC and PL	Regarding the use of Komboglyze and Onglyza in older patients, no dose adjustment is recommended based solely on age. No dose adjustment is recommended for patients with mild renal impairment. The dose should be reduced to 2.5 mg once daily in patients with moderate or severe renal

	SmPC with regard to posology recommendations and warnings for use in elderly patients and patients with renal impairment, minor amendment of the existing warning on skin disorders, lack of inhibition of CYP2C8 by saxagliptin and inclusion of safety and efficacy information from study D1680C00003 (SAVOR), a cardiovascular outcome study, and study D1680L00002 (GENERATION), a study comparing saxagliptin with glimepiride in elderly patients. Furthermore, the MAH took the opportunity to implement QRD version 9 for Komboglyze and to update the list of local representatives and to perform minor editorial corrections throughout both PIs. 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 new quality, preclinical, clinical or pharmacovigilance data				impairment. Onglyza is not recommended for patients with end stage renal disease (ESRD) requiring haemodialysis. Experience in NYHA class III-IV of heart failure is still limited. Therefore, caution is warranted in these patients. In the SAVOR trial a small increase in the rate for hospitalisation for heart failure was observed in the saxagliptin treated patients compared to placebo (see section 5.1). Additional analysis did not indicate a differential effect among NYHA classes. In in vitro studies, saxagliptin and its major metabolite did not inhibit CYP2C8. SAVOR was a cardiovascular outcome study conducted in 16,492 patients with type II diabetes who had a history of, or were at risk for, cardiovascular events. Its results demonstrated that saxagliptin is non-inferior to placebo and does not induce an increased risk for cardiovascular death, non-fatal myocardial infarction or non-fatal ischaemic stroke. GENERATION was a 52-week trial performed in 720 elderly patients. The purpose was to evaluate whether saxagliptin + Metformin was superior to glimepiride + metformin on the primary endpoint of subjects reaching HbA1c < 7% without hypoglycaemia (confirmed or severe). There appeared to be no difference in responders. Glimepiride was more effective than saxagliptin in reducing HbA1c, but at the cost of more hypoglycaemia. Saxagliptin was less effective, but can still reduce HbA1c to some extent, and did not induce hypoglycaemia. Age appeared to be an important factor: results favoured saxagliptin in subjects < 75, and glimepiride in subjects > 75 years.

R/0023	Renewal of the marketing authorisation.	22/05/2014	18/07/2014	SmPC and PL	Onglyza (saxagliptin) is a DPP-4 inhibitor intended for use in patients with type 2 diabetes, initially authorized as add-on treatment to metformin, a sulphonylurea or thiazolidinedione. During the 5 year renewal period since launch of Onglyza (saxagliptin), additional data from studies became available and led to the extension of the indication of the product for the use as monotherapy in patients for whom metformin is inappropriate, triple oral therapy in combination with metformin plus a sulphonylurea, and combination therapy with insulin. There is no evidence of any subgroup differential benefit for any of the treatments. Since the initial Marketing Authorisation the product information has been updated with information on hypersensitivity reactions, pancreatitis, nausea, dermatitis, pruritus and abdominal pain. The benefit-risk balance of Onglyza in the treatment of type 2 diabetes remains favourable and therefore the renewal of the marketing authorisation with unlimited validity is recommended.
WS/0528	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 in order to implement the recommendations of an Art 5(3) procedure on GLP-1-based therapies and pancreatic safety. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/06/2014	15/10/2014	SmPC and PL	In this variation the Product information of Komboglyze and Onglyza has been updated with additional information related to the use of these products in patients with history of pancreatic disease and with advice on seeking medical help in cases of signs and symptoms of pancreatitis.

PSUV/0022	Periodic Safety Update	20/02/2014	23/04/2014	SmPC and PL	Section 4.8 of the SmPC should be updated by adding 'diarrhoea' as adverse reaction with a frequency of 'common'. The Package leaflet should be updated accordingly. The update of this section is based on two cases from clinical trials with positive de- and rechallenge plus 11 spontaneously reported cases with factors of positive de- and/or rechallenges, and given that it is a known ADR for the other DPP4-inhibitors as well. In regard to the assigned frequency, a total of 106 ADRs of diarrhoea were reported in 2042 patients in a 5-study pooled safety analysis. In a 20-study pooled from Hirshberg et al, 63 ADRs of diarrhoea were reported in 978 patients. Diarrhoea should therefore be ranked under the frequency of 'common (≥1/100 to <1/10)' according to the guidance provided in the SmPC Guideline.
WS/0416/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 an alternate manufacturer of the active substance Saxagliptin and intermediates To increase the maximum batch size of an intermediate To increase the maximum batch size of the active substance Saxagliptin 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	19/09/2013	n/a		

	manufacturer B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size B.I.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				
II/0018	Update of sections 4.1and 5.1 of the SmPC in order to extend the indication to include monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance . The Package Leaflet is updated accordingly. 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 9.0. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	27/06/2013	26/07/2013	SmPC, Annex II and PL	For further information please refer to the scientific conclusion: H-1039-VAR-II-18.
IG/0259	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/01/2013	n/a		
WS/0295	This was an application for a variation following a worksharing procedure according to Article 20 of	17/01/2013	18/02/2013	SmPC, Annex II, Labelling	For further information please refer to the scientific conclusion: H-2059-VAR-WS-295-en for Komboglyze and

	Commission Regulation (EC) No 1234/2008. Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to extend the indication for Onglyza and Komboglyze to include combination of metformin, a suphonylurea and saxagliptin, i.e. triple oral therapy. The Package Leaflet and Labelling are updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 8.2. Furthermore, in the SmPC and the Package Leaflet minor typographical errors were corrected and these were harmonized for the two products. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			and PL	H-1039-VAR-WS-295-en for Onglyza.
IA/0016	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/01/2012	n/a		
II/0014	Update following assessment of PSUR 3 of section 4.4 of the SmPC in order to add a warning on pancreatitis as well as update of section 4.8 with regard to additional adverse reactions (nausea, pancreatitis, dermatitis, pruritus). The Package Leaflet was updated in accordance. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a	17/11/2011	22/12/2011	SmPC and PL	Section 4.4 and 4.8 of the SmPC were updated with new information based largely on accumulated case reports of Onglyza. Case reports of patients with nausea who experienced a positive rechallenge with Onglyza were indicative of a causal relationship, and since nausea can be expected to occur with saxagliptin since 'vomiting' is a listed reaction, nausea is now included in section 4.8 of the SmPC. The

	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				frequency of nausea has been calculated based on an analysis of clinical trial data with a frequency in all saxagliptin treatment groups of 2.2% (common). Pancreatitis has been reported infrequently with the use of Onglyza. However, although there have been confounding co-medications and/or underlying diseases, in several patients signs of pancreatitis occurred after start of saxagliptin and resolved after discontinuation, suggestive of a causal relationship. Moreover, pancreatitis has been recognized as an adverse event for other DPP-4 inhibitors. Therefore, information about pancreatitis is now included in the SmPC in section 4.4 as a warning and in section 4.8 to include pancreatitis as adverse reaction, with the frequency "uncommon". Dermatitis and pruritus are now included as adverse reactions in section 4.8 of the SmPC, with the frequencies of these reactions calculated based on a pooled analysis of clinical trial data. The frequency of dermatitis in all saxagliptin treatment groups was 0.3% (uncommon). The frequency of pruritus in all saxagliptin treatment groups was 0.7% (uncommon). This followed the more detailed analysis of cumulative data of skin reactions (erythema, eczema, rash, allergic dermatitis).
II/0011	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/10/2011	22/11/2011	PL	
IA/0015	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold	28/10/2011	n/a		

	increase compared to the currently approved batch size				
II/0012	Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet regarding hypersensitivity reactions. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/09/2011	24/10/2011	SmPC, Annex II, Labelling and PL	The MAH applied for this type II variation to include information in line with the recently updated Company Core Data Sheet. The MAH is amending sections 4.3 (contra-indications), 4.4 (warnings/precautions) and 4.8 (undesirable effects) of the SPC. The package leaflet has also been updated accordingly.
IB/0013	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	28/06/2011	n/a		
IA/0010	C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	08/04/2011	n/a		
X/0004	Annex I_2.(c) Change or addition of a new strength/potency	16/12/2010	28/02/2011	SmPC, Annex II, Labelling and PL	
II/0008	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	28/02/2011	SmPC, Labelling and PL	
IA/0009/G	This was an application for a group of variations.	29/10/2010	n/a	Annex II	

	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 C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV				
II/0006	Update of section 5.1 of the Summary of Product Characteristics to include the results of a study to evaluate the efficacy and safety of saxagliptin in combination with metformin compared with sitagliptin with metformin. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/07/2010	06/09/2010	SmPC	An 18-week study was conducted to evaluate the efficacy and safety of saxagliptin 5 mg in combination with metformin (403 patients), compared with sitagliptin 100 mg in combination with metformin (398 patients) in 801 patients with inadequate glycaemic control on metformin alone. After 18 weeks, saxagliptin was non-inferior to sitagliptin in mean reduction from baseline in HbA1c in both the per-protocol and the full analysis sets . The reductions from baseline in HbA1c respectively for saxagliptin and sitagliptin in the primary per-protocol analysis were -0.5% (mean and median) and -0.6% (mean and median). In the confirmatory full analysis set, mean reductions were -0.4% and -0.6% respectively for saxagliptin and sitagliptin, with median reductions of -0.5% for both groups. Section 5.1 of the SPC have been updated to reflect the results of the study.
II/0005	Update of section 5.1 of the Summary of Product Characteristics (SPC) to reflect the results of an active controlled study to evaluate the efficacy and safety of saxagliptin in combination with metformin compared with sulphonylurea in combination with	22/07/2010	06/09/2010	SmPC	A 52-week study was conducted to evaluate the efficacy and safety of saxagliptin 5 mg in combination with metformin (428 patients) compared with sulphonylurea (glipizide, 5 mg titrated as needed to 20 mg, mean dose of 15 mg) in combination with metformin (430 patients) in

	metformin. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				858 patients with inadequate glycaemic control (HbA1c 6.5%-10%) on metformin alone. The mean metformin dose was approximately 1900 mg in each treatment group. After 52 weeks, the saxagliptin and glipizide groups had similar mean reductions from baseline in HbA1c in the per-protocol analysis (-0.7% vs. -0.8%, respectively, mean baseline HbA1c of 7.5% for both groups). The intent-to-treat analysis showed consistent results. The reduction in FPG was slightly, less in the saxagliptin-group and there were more discontinuations (3.5% vs 1.2%) due to lack of efficacy based on FPG criteria during the first 24 weeks of the study. Saxagliptin also resulted in a significantly lower proportion of patients with hypoglycaemia, 3% (19 events in 13 subjects) vs. 36.3% (750 events in 156 patients) for glipizide. Patients treated with saxagliptin exhibited a significant decrease from baseline in body weight compared to a weight gain in patients administered glipizide (- 1.1 vs. +1.1 kg). Section 5.1 of the SPC was updated to reflect the results of this study.
II/0007	Update of section 5.1 of the Summary of Product Characteristics (SPC) to reflect long-term data from a study to evaluate the efficacy and safety of saxagliptin add-on to glibenclamide, a study to evaluate the efficacy and safety of saxagliptin add-on to thiazolidinedione therapy and a study to evaluate the efficacy and safety of saxagliptin in combination with metformin as initial therapy. In addition the MAH made amendments in section 5.1 of the SPC regarding the information on saxagliptin add-on to metformin therapy study.	20/05/2010	02/07/2010	SmPC, Annex II, Labelling and PL	At the time of the initial Marketing Authorisation (MA) the MAH committed to submit long-term data from the core studies CV181040 (FUM 006), CV181013 (FUM 007) and CV181039 (FUM 009). These studies were conducted to evaluate the efficacy and safety of saxagliptin add-on to glibenclamide, saxagliptin add-on to thiazolidinedione therapy and saxagliptin in combination with metformin as initial therapy, respectively. The CHMP concluded for study CV181040 that the addition of saxagliptin to glyburide provided a sustained reduction in glycaemic parameters, including HBA1C and PPG, when

	The MAH took the opportunity to update the SPC, Labelling and Package Leaflet in line with the latest version of the QRD templates and to update the details of the local representatives in the Package Leaflet. The MAH also changed the version number of the Pharmacovigilance System in Annex II to reflect the version number of the latest approved Pharmacovigilance System. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				compared with treatment with uptitrated glyburide, without an increase in hypoglycaemia or hypoglycaemic symptoms. However results after 76 weeks of therapy indicate that diabetic control as assessed with HbA1C is not adequate anymore, but is still better than Glyburide alone. Saxagliptin was well tolerated. For study CV181013 the CHMP concluded that the results of the long-term analysis of this study demonstrate that the administration of saxagliptin as add on therapy to background treatment with a thiazolidinedione (TZD) with or without rescue with metformin for up to 76 weeks was well tolerated. The addition of saxagliptin to TZD provided a long term reduction in glycaemic parameters, including HBA1C, FPG, and PPG, when compared with treatment with a TZD alone, without an increase in hypoglycaemia or hypoglycaemic symptoms. For study CV181039 the CHMP concluded that the addition of saxagliptin to metformin provided a sustained reduction in glycaemic parameters, including HBA1C, FPG, and PPG, without an increase in hypoglycaemia or hypoglycaemic symptoms. The difference in change in HbA1C was statistically significant compared to metformin, but the 95% CI is wide and the clinical relevance debatable. The results of the long-term analysis of this study demonstrate that the administration of saxagliptin as initial combination therapy with metformin or as initial monotherapy for up t
IA/0003	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s)	22/03/2010	n/a	Annex II	

	to the DDPS that does not impact on the operation of the pharmacovigilance system				
IA/0002	C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	22/03/2010	n/a	Annex II	
IA/0001	IA_09_Deletion of manufacturing site	25/11/2009	n/a		