EMA/179393/2021

Glubrava

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/1979/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.	04/02/2021		SmPC, Annex II, Labelling and PL	

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

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	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation A.1 - Administrative change - Change in the name and/or address of the MAH				
WS/1680	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of an updated RMP (version 27.1) in order to update and consolidate within a single RMP the RMPs for Pioglitazone, Pioglitazone/Metformin fixed dose combination (FDC) and Pioglitazone/Glimepiride FDC. The list of safety concerns has also been reviewed and consolidated RMP version updated with information agreed/approved as part of the PSUR procedure (EMEA/H/C/PSUSA/00002417/201807) with regards to discontinuation of pioglitazone aRMMs. 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	28/11/2019	n/a		
IG/1101	A.7 - Administrative change - Deletion of manufacturing sites	08/08/2019	n/a		
PSUSA/2417/ 201807	Periodic Safety Update EU Single assessment - glimepiride / pioglitazone hydrochloride, metformin /	28/03/2019	06/06/2019	Annex II	Please refer to PSUSA-00002417-201807 EPAR:

	pioglitazone, pioglitazone				Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
WS/1485/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 or intermediate product - Minor change in the manufacturing process	13/12/2018	n/a		
WS/1386	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	25/05/2018	n/a		
WS/1388/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.	25/05/2018	n/a		

	A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites 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				
WS/1294	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	14/12/2017	n/a		
R/0054	Renewal of the marketing authorisation.	14/09/2017	10/11/2017	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Glubrava in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
WS/1138	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	11/05/2017	n/a		

IG/0787/G	This was an application for a group of variations. 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 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	31/03/2017	n/a		
IG/0779/G	This was an application for a group of variations. 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 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 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 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	16/03/2017	n/a		

	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				
PSUSA/2417/ 201607	Periodic Safety Update EU Single assessment - glimepiride / pioglitazone hydrochloride, metformin / pioglitazone, pioglitazone	09/03/2017	n/a		PRAC Recommendation - maintenance
IG/0766	A.7 - Administrative change - Deletion of manufacturing sites	02/02/2017	n/a		
WS/0991	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	26/01/2017	n/a		Pioglitazone_5018 is a nested case-control study to further investigate a potential association between pioglitazone use and prostate cancer, using the CPRD GOLD database. The study was specifically designed to evaluate the risk of prostate cancer with use of pioglitazone in male patients with T2DM.Additionally, data on the incidence of adjudicated prostate cancer in patients receiving pioglitazone in the long-term Insulin Resistance Intervention after Stroke (IRIS) trial (IRIS Report) have also been provided. The results of this study did not show a statistically significant association between pioglitazone and prostate cancer. The MAH provided available histological data on cases of prostate cancer. Though the available data is very limited, the results of the histological data from all sources available to the MAH (Safety database, Pioglitazone_5018, PROactive Extension study and IRIS study) suggest that the majority of prostate cancers are prostatic adenocarcinomas in keeping with the common histological type seen in prostate cancer. Though the available data is

					very limited, there remain uncertainties in relation to any causal association between prostate cancer and pioglitazone therapy. The Marketing Authorisation Holder will continue to closely monitor this issue and will report should relevant data emerge.
A31/0045	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/0739/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release 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	30/11/2016	10/11/2017	Annex II and PL	

	from an already approved manufacturer 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 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 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				
WS/0990	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	13/10/2016	n/a		
PSUSA/2417/ 201507	Periodic Safety Update EU Single assessment - glimepiride / pioglitazone hydrochloride, metformin / pioglitazone, pioglitazone	01/04/2016	26/05/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2417/201507.
WS/0848	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the section 4.4 of the SmPC based on results of two long-term observational cohort studies	28/04/2016	12/12/2016	SmPC and PL	As a result of this variation the Product information has been updated to reflect the fact that although some epidemiological studies have suggested a small increased risk of bladder cancer in diabetic patients treated with pioglitazone, not all of them identified a statistically

	assessing bladder cancer risk with pioglitazone. The RMP has been updated accordingly. Furthermore, minor editorial changes were introduced in the PI. In addition, the MAH took the opportunity to update the details 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				significant increased risk.
WS/0875	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	01/04/2016	n/a		
WS/0827	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of final results from observational study PROactive together with post hoc analysis of KPNC and comprehensive review of the data on prostate cancer risk. The RMP is updated accordingly and RMP versions 22.1 of Actos, Glustin, Competact and Glubrava and RMP version 20.1 of Tandemact are acceptable. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	25/02/2016	n/a		n/a

	of studies to the competent authority				
IG/0652	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	22/01/2016	n/a		
WS/0705	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To change the due date for reporting of the Pan-European multiple database bladder cancer risk characterisation study ER12-9433 from 30 December 2014 to 31 July 2015. In addition, an administrative change has been introduced to include mention of a Drug Utilization Study using the medical registries in Denmark (Pioglitazone 5019) and associated timelines. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/05/2015	n/a		
PSUSA/2417/ 201407	Periodic Safety Update EU Single assessment - glimepiride / pioglitazone hydrochloride, metformin / pioglitazone, pioglitazone	12/03/2015	n/a		PRAC Recommendation - maintenance
WS/0646	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	20/11/2014	n/a		

	Submission of the study AD-4833-411, a study on the utilization of pioglitazone in clinical practice in the UK after the product information update in July 2011, and updated RMP in order to reflect the finalisation of the study. The MAH takes the occasion to implement in the RMP already agreed administrative information. The requested worksharing procedure leads to amendments to the Risk Management Plan (RMP). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
WS/0647	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 study 01-03-TL-OPI-524, Cohort Study of Pioglitazone and Bladder Cancer in Patients with Diabetes, and updated RMP in order to reflect the finalisation of the study. The MAH takes the occasion to implement in the RMP already agreed administrative information. The requested worksharing procedure proposed amendments to the Risk Management Plan (RMP). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	20/11/2014	n/a		

WS/0609	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	25/09/2014	n/a		
WS/0541	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The WSA submitted the final analysis report of the KPNC non-bladder malignancy study extension (AD4833-403) and an updated Risk Management Plan to reflect the final study results. The requested worksharing procedure proposed no amendments to the PI. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/09/2014	n/a		N/A
IB/0033/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/07/2014	29/07/2015	SmPC, Annex II, Labelling and PL	

PSUSA/2417/201307	Periodic Safety Update EU Single assessment - glimepiride / pioglitazone hydrochloride, metformin / pioglitazone, pioglitazone	06/03/2014	n/a		PRAC Recommendation - maintenance
IG/0401	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	11/02/2014	n/a		
PSUV/0029	Periodic Safety Update	19/09/2013	13/11/2013	SmPC and PL	For further information please refer to: Glubrava-H-C-893-Grounds PSUV-29-en.
WS/0413	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To introduce an alternative size for the immediate packaging of the active substance (pioglitazone). B.I.c.2.z - Change in the specification parameters and/or limits of the immediate packaging of the AS - Other variation	19/09/2013	n/a		
IG/0307	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	04/06/2013	n/a		
T/0026	Transfer of Marketing Authorisation	25/03/2013	29/04/2013	SmPC, Labelling and PL	Transfer of the Marketing Authorisation to Takeda Pharma A/S, Denmark.

IG/0267/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.I.c.2.z - Change in the specification parameters and/or limits of the immediate packaging of the AS - Other variation	12/02/2013	n/a		
IG/0231	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/11/2012	n/a		
WS/0324	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC, upon request by the CHMP following the assessment of the 25th PSUR for pioglitazone, in order to update the safety information regarding hypersensitivity and allergic reactions. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the SmPC and Package Leaflet, and to update the list of local representatives for the Portuguese representative in the Package Leaflet for Glustin. This variation followed a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	15/11/2012	18/12/2012	SmPC and PL	The following information was included in the SmPC as part of this procedure: Post-marketing reports of hypersensitivity and allergic reactions in patients treated with pioglitazone have been reported. These reactions include anaphylaxis, angioedema, and urticaria. The frequency of these adverse reactions is unknown.

	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				
R/0020	Renewal of the marketing authorisation.	19/07/2012	17/09/2012	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Glubrava remains positive, but considers that its safety profile is to be closely monitored for the following reasons: The CHMP has reviewed the totality of the available data on pioglitazone, including preclinical studies, clinical studies, post-marketing data and epidemiological studies within an Art. 20 referral procedure and concluded that the available data consistently identified a small increased risk of bladder cancer associated with the use of pioglitazone, and recommended that the product information should include further restrictions of use. Moreover a need for further analysis of the risk of bladder cancer associated with pioglitazone use was identified and studies to that goal are now included in the Risk Management Plan, for which reporting is expected during the next few years. The CHMP decided that the MAH should continue to submit 6-monthly PSURs. Therefore, based upon the safety profile of Glubrava, which requires the submission of 6-monthly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time. During the renewal procedure, changes were made to the Product Information to bring it in line with the current

					EMA/QRD template, SmPC guideline and other relevant guidelines, which were reviewed by QRD and accepted by the CHMP.
IA/0022/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	13/07/2012	n/a		
IG/0179	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	30/05/2012	n/a		
IAIN/0019/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.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	22/03/2012	n/a		
A20/0015	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the CHMP to assess the safety concern of bladder cancer	20/10/2011	22/12/2011		Please refer to the CHMP Assessment Report: Revised Assessment Report for Actos, Glustin, Competact, Glubrava, Tandemact Article 20 procedures

	and its impact on the benefit-risk balance of the centrally authorised products containing pioglitazone. The European Commission requested the Committee to give its opinion as to whether measures are necessary to ensure the safe use of these medicinal products and specifically on whether the marketing authorisation should be maintained, varied, suspended or withdrawn.				(EMEA/H/C/0285/A-20/0046; EMEA/H/C/0286/A-20/0044; EMEA/H/C/0665/A-20/0030; EMEA/H/C/0893/A-20/0015; EMEA/H/C/0680/A-20/0022)
IG/0130/G	This was an application for a group of variations. 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 B.III.1.a.3 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	16/12/2011	n/a		
IG/0071/G	This was an application for a group of variations. 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 B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-	14/06/2011	n/a		

	significant specification parameter (e.g. deletion of an obsolete parameter) 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.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.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)				
IB/0013/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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure A.7 - Administrative change - Deletion of manufacturing sites 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	01/09/2010	n/a		

II/0012	Update of SPC and Labelling Update of section 5.3 of the SPC upon request by CHMP following the assessment of FU2 033.3, to reflect the results of the mechanistic study in rats that was undertaken to investigate the mechanisms responsible for an increased incidence of hyperplasia and tumours of the urinary bladder epithelium in rats treated with pioglitazone for up to 2 years. In addition, the MAH table the opportunity to implement some minor changes in the labelling in line with the latest QRD template. Update of Summary of Product Characteristics	18/02/2010	30/03/2010	SmPC and Labelling	Prior to the initial submission of pioglitazone to EU regulatory authorities, 2 year bioassays in the rat and mouse determined pioglitazone treatment to be associated with urinary bladder tumours in the male rat. Pioglitazone and its major metabolites were not genotoxic, as established in a comprehensive battery of genotoxicity assays. Through re-examination of retained bladder specimens in fixative, calculi were found in the bladder and it was hypothesized that urinary calculi formation with subsequent irritation, hyperplasia and metaplasia may be responsible for the carcinogenic responses observed in male rats. It was concluded that the administration of pioglitazone may be directly responsible for an increased incidence of hyperplastic changes in the bladder of the rat. The presence of microcrystals exacerbates the hyperplastic response but is not considered to be the cause of the hyperplastic changes. Updated part of Section 5.3 of the Summary of Product Characteristic: Pioglitazone was devoid of genotoxic potential in a comprehensive battery of in vivo and in vitro genotoxicity assays. An increased incidence of hyperplasia (males and females) and tumours (males) of the urinary bladder epithelium was apparent in rats treated with pioglitazone for up to 2 years. The formation and presence of urinary calculi with subsequent irritation and hyperplasia was postulated as the mechanistic basis for the observed tumourigenic response in the male rat. A 24-month mechanistic study in male rats demonstrated that administration of pioglitazone resulted

					in an increased incidence of hyperplastic changes in the bladder. Dietary acidification significantly decreased but did not abolish the incidence of tumours. The presence of microcrystals, although exacerbating the hyperplastic response is not considered to be the primary cause of the hyperplastic changes. The relevance to humans of the tumourigenic findings in the male rat cannot be excluded. There was no tumorigeni
II/0011	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Annex II has been updated in line with the QRD requirements for the Risk Management Plan and the Pharmacovigilance System including the new version number of the DDPS. Minor corrections were also included in the Summary of Product Characteristics. Update of Summary of Product Characteristics	23/07/2009	17/09/2009	SmPC, Annex II and PL	The MAH updated its Pharmacovigilance System and submitted therefore a type II variation. The CHMP considered that the Pharmacovigilance System as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
II/0010	Update of the Summary of Product Characteristics (SPC) to reflect data from the OPIMET study investigating the safety and efficacy of the Fixed Dose Combination tablet of pioglitazone and metformin. Sections 4.8 and 5.1 of the SPC have been updated. Update of Summary of Product Characteristics	23/07/2009	17/09/2009	SmPC	The MAH has completed the first clinical study (OPIMET-008) to compare the efficacy and safety of the pioglitazone/metformin FDC tablet therapy with each of its components in subjects with type 2 diabetes mellitus. The fixed dose combination tablet of pioglitazone 15 mg/metformin 850 mg BID (N=201), pioglitazone 15 mg BID (N=189), and metformin 850 mg BID (N=210) were evaluated in type 2 diabetes mellitus patients with mean baseline HbA1C of 9.5% in a randomised double-blind, parallel-group study. Previous anti-diabetic medication was discontinued for 12 weeks prior to baseline measurements. After 24 weeks of treatment, the primary endpoint of mean change from baseline in HbA1c was -1.83% in the

					combination group versus -0.96% in the pioglitazone group (p<0.0001) and -0.99% in the metformin group (p<0.0001). The safety profile seen in this study reflected the known adverse reactions seen with the individual products and did not suggest any new safety issues. Sections 4.8 and 5.1 of the SPC have been updated.
IA/0009	IA_01_Change in the name and/or address of the marketing authorisation holder	11/02/2009	n/a	SmPC, Labelling and PL	
N/0007	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/12/2008	n/a	PL	
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/08/2008	n/a	PL	
IA/0006	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	09/07/2008	n/a		
IB/0001	IB_02_Change in the name of the medicinal product	25/01/2008	n/a	SmPC, Annex II, Labelling and PL	
IA/0004	IA_05_Change in the name and/or address of a manufacturer of the finished product	11/01/2008	n/a		
IA/0003	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	11/01/2008	n/a		
IA/0002	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	11/01/2008	n/a		
