Competact

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
IA/0081/G	This was an application for a group of variations. B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) A.7 - Administrative change - Deletion of manufacturing sites	11/08/2023		SmPC, Labelling and PL	

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

	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)				
IB/0080/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 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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	08/05/2023	n/a		
PSUSA/2417/ 202107	Periodic Safety Update EU Single assessment - glimepiride / pioglitazone hydrochloride, metformin / pioglitazone, pioglitazone	10/03/2022	n/a		PRAC Recommendation - maintenance
T/0077	Transfer of Marketing Authorisation	03/06/2021	21/06/2021	SmPC, Labelling and PL	

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. 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	04/02/2021	21/06/2021	SmPC, Annex II, Labelling and PL	
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 / pioglitazone, pioglitazone	28/03/2019	22/05/2019	Annex II	Please refer to PSUSA-00002417-201807 EPAR: 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/1443	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	20/09/2018	22/05/2019	SmPC, Annex II, Labelling and PL	
WS/1386	This was an application for a variation following a worksharing procedure according to Article 20 of	25/05/2018	n/a		

	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				
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. 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	25/05/2018	n/a		
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		
WS/1138	This was an application for a variation following a	11/05/2017	n/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				
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	16/03/2017	n/a		

	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				
PSUSA/2417/ 201607	Periodic Safety Update EU Single assessment - glimepiride / pioglitazone hydrochloride, metformin / pioglitazone, pioglitazone	09/03/2017	n/a		PRAC Recommendation - maintenance
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.
A31/0060	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 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	30/11/2016	30/10/2017	Annex II and PL	
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/	Periodic Safety Update EU Single assessment -	01/04/2016	26/05/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending

201507	glimepiride / pioglitazone hydrochloride, metformin / pioglitazone, pioglitazone				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 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	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 significant increased risk.
R/0057	Renewal of the marketing authorisation.	25/02/2016	25/04/2016	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 Competact in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
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 of studies to the competent authority	25/02/2016	n/a		n/a
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	21/05/2015	n/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				
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. 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	20/11/2014	n/a		
WS/0647	This was an application for a variation following a	20/11/2014	n/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				
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	25/09/2014	n/a		N/A

	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				
IB/0047/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	23/07/2014	03/07/2015	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/0043	Periodic Safety Update	19/09/2013	13/11/2013	SmPC and PL	For further information please refer to: Competact-H-C-655-Grounds PSUV-43-en.
WS/0413	This was an application for a variation following a worksharing procedure according to Article 20 of	19/09/2013	n/a		

	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				
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/0040	Transfer of Marketing Authorisation	25/03/2013	17/04/2013	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. 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	15/11/2012	20/12/2012	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.
IA/0036/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished	12/07/2012	n/a		

	product - Minor changes to an approved test procedure				
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/0034/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 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		
A20/0030	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the CHMP to assess the safety concern of bladder cancer 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	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 (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)

	authorisation should be maintained, varied, suspended or withdrawn.				
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-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-	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)				
R/0028	Renewal of the marketing authorisation.	17/03/2011	27/05/2011	SmPC, Annex II, Labelling and PL	Based on the review of the available information, the CHMP is of the opinion that the quality, the safety and the efficacy of Competact continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of this medicinal product continues to be favourable but considers that its safety profile is to be closely monitored for the following reasons: The use of pioglitazone/metformin is associated with a number of identified adverse events (cardiac failure, weight gain, macular oedema, lactic acidosis, hypoglycaemia and bone fractures) as well as potential risks (hepatic events, carcinogenicity in particular bladder cancer, rhabdomyolysis, anaphylactoid reactions, blood disorders, cerebrovascular ischaemia, cardiac ischaemia) to be closely monitored and to be reported in 6 monthly PSURs and included in the Risk Management Plan. Further data and results from several studies are expected to further evaluate the risk of bladder cancer. Also study

					data are awaited to provide further answers on the risk of bone fractures. Therefore, based upon the safety profile of Competact, which requires the submission of 6 monthly PSURs, the CHMP concluded that the MAH should, on the basis of pharmacovigilance grounds, 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 EMEA/QRD template, SmPC guideline and other relevant guidelines, which were reviewed by QRD and accepted by the CHMP. In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Belgium, Luxembourg, Denmark, Norway and Sweden. Annex II has been amended to reflect the need for 6 monthly PSUR submissions.
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/03/2011	n/a	PL	
IA/0029	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	03/03/2011	03/03/2011	SmPC, Labelling and PL	
IB/0026/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure A.7 - Administrative change - Deletion of manufacturing sites	01/09/2010	n/a		

	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 B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IB/0025/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	03/06/2010	03/06/2010	SmPC, Labelling and PL	
II/0024	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.	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

	Update of Summary of Product Characteristics				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/0023	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	23/07/2009	21/08/2009	SmPC and Annex II	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

	Pharmacovigilance System including the new version number of the DDPS. Minor corrections were also included in the Summary of Product Characteristics. Update of DDPS (Pharmacovigilance)				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/0022	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	21/08/2009	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.
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/04/2009	n/a	PL	
IA/0021	IA_01_Change in the name and/or address of the marketing authorisation holder	17/02/2009	n/a	SmPC, Labelling and	

				PL	
IA/0018	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		
IA/0017	IA_05_Change in the name and/or address of a manufacturer of the finished product	13/12/2007	n/a		
IA/0016	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	07/12/2007	n/a		
IA/0015	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	07/12/2007	n/a		
II/0013	Update of section 4.3 of the Summary of Products Characteristics (SPC) to remove the contraindication for the use of pioglitazone in combination with insulin. Sections 4.4, 4.8 and 5.1 of the SPC have been consequently updated to add information on the risk of heart failure. The relevant sections of the Package Leaflet have been updated accordingly. Additionally, Annex II was updated to reflect the revision of the Risk Management Plan. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	24/10/2007	SmPC, Annex II and PL	The MAH submitted this Type II variation to remove the contraindication for the use of pioglitazone in combination with insulin, primarily as a result of clinical trial data from the completion of a large macrovascular outcome study of pioglitazone in patients with type 2 diabetes mellitus, known as 'PROactive' (protocol reference AD-4833/EC444), performed following a commitment made to the CPMP in June 2000. The MAH also submitted, as part of the present variation application, data from three efficacy and safety studies of pioglitazone used in combination with insulin. The main concern of the CHMP was the fact that both insulin and pioglitazone alone are associated with fluid retention and heart failure. However, it appears that combination therapy with pioglitazone and insulin is associated with an increased risk of heart failure, but not

					an increase in mortality, in particular from the sequelae of heart failure. The degree of heart failure would most likely be mild, and could be monitored symptomatically or by weight gain. Therefore, the CHMP concluded that the exposure data presented was adequate to support the deletion of the contraindication with insulin, provided that the risk of heart failure is reflected in detail in the product information and in the Risk Management Plan. Section 4.3 of the Summary of Products Characteristics was updated to remove the contraindication for the use of pioglitazone in combination with insulin. Sections 4.4, 4.8 and 5.1 were consequently updated to add information on the risk of heart failure. The relevant sections of the Package Leaflet were updated accordingly.
II/0012	Update of section 5.1 of the SPC to describe the results of a large macrovascular outcome study of pioglitazone in patients with type 2 diabetes mellitus (PROactive study). Section 4.4 has been updated to add information on the risk of heart failure, as per the results of the mentioned study. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	24/10/2007	SmPC	At the time of the original Marketing Authorisation of Actos (pioglitazone), the MAH committed to perform a large macrovascular outcome study of pioglitazone in patients with type 2 diabetes mellitus. The MAH submitted the results of this macrovascular outcome study (PROactive study). The PROactive study failed regarding it's pre-specified primary endpoint, and any benefit suggested by the secondary endpoint suggests an effect in a type 2 diabetic population with extensive disease and being treated concurrently with multiple anti-diabetic and cardiovascular medicines, and treated with 45mg of pioglitazone. As would be expected, there were increases in weight in the pioglitazone group, and an increase in hypoglycaemia corresponding with better control of diabetes. There was also an increase in cardiac failure in the pioglitazone group.

					Although these were no new safety issues, the previous safety concerns relating to weigh gain, oedema and heart failure were confirmed. Although the PROactive study suggested that administration of pioglitazone was not associated with an increased cardiovascular risk, the study failed to document a clear benefit, and the safety concerns mentioned above remain, particularly in the context of the new indication of pioglitazone in combination with insulin. The CHMP agreed that some information on the PROactive study, which was a significant and well-conducted study, could be introduced in section 5.1 of the Summary of Product Characteristics.
IB/0014	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	24/08/2007	n/a		
II/0007	Update of the Summary of Product Characteristics (SPC) and Package Leaflet (PL) to include information on the risk of bone fractures in female patients treated with pioglitazone. Update of Summary of Product Characteristics and Package Leaflet	24/05/2007	20/08/2007	SmPC and PL	Further to the review of available information on increased incidence of fractures among female patients with type 2 diabetes taking a TZD, the CHMP was of the view that this issue should be further investigated and requested the Marketing Authorisation Holder (MAH) to provide information on all cases of fractures in patients taking pioglitazone, as well as an overview of all clinical and non-clinical studies with glitazones in which bone metabolism was investigated or in which an effect on bone has been reported. Upon evaluation of the data provided by the MAH, the CHMP was of the view that there are theoretical reasons why thiazolidinediones could be associated with increased risk of fracture. Severity and duration of diabetes are risks factors for osteoporosis, and it is difficult to draw

					conclusions from the post-marketing data as fractures not surprisingly occur in older female patients. However, considering the clinical trial database, there appears to be a small but definite increased risk of fracture in the female patients treated with pioglitazone and analyses of the pooled data from controlled, double-blind, randomised, comparative clinical studies suggest a relative increase in fracture risk with time. Based on the available data, the CHMP requested the MAH to update the product information for Actos to reflect the risk of bone fractures. Sections "Special warnings and precautions for use" and "Undesirable effects" of the Summary of Product Characteristics (SPC) were updated with the available data from clinical trials regarding bone fractures and with a warning reflecting that the risk of fractures should be considered in the long-term care of women treated with pioglitazone. The Package Leaflet was updated accordingly.
IA/0011	IA_36_ b_Change in shape or dimensions of the container/closure - other pharm. forms	12/07/2007	n/a		
IB/0008	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	10/07/2007	n/a	SmPC	
IA/0010	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	10/07/2007	n/a	Annex II and PL	
IA/0009	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	10/07/2007	n/a		

N/0006	Update of the local representatives in Section 6 of the PL (Package Leaflet) to change the details of the local representatives in the following Member States: Belgium, Czech Republic, Denmark, Estonia, Finland, Greece, Iceland, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Portugal, Romania, Spain, Slovakia, Slovenia and Sweden. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/03/2007	n/a	PL	
IB/0004	IB_10_Minor change in the manufacturing process of the active substance	30/01/2007	n/a		
N/0003	The Marketing Authorisation Holder applied for an update of the details of the local representative in Ireland. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/01/2007	n/a	PL	
IA/0005	IA_13_a_Change in test proc. for active substance - minor change	09/01/2007	n/a		
II/0001	Update of sections 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction) and 5.2 (Pharmacokinetic properties sections) of the Summary of Product Characteristics (SPC) to reflect information regarding the potential interaction between pioglitazone and gemfibrozil and	16/11/2006	04/01/2007	SmPC and PL	The MAH applied for this variation to reflect potential interactions with gemfibrozil and with rifampicin based on the publication of 3 drug-interactions studies describing the effect of CYP2C8 inhibition or induction on the pharmacokinetics of pioglitazone in humans. Jaakola et al. 2005 study demonstrated that gemfibrozil

	pioglitazone and rifampicin. In addition the Package Leaflet has been updated to include the details of the Bulgarian and Romanian local representatives. Update of Summary of Product Characteristics and Package Leaflet				raised the mean total area under the plasma concentration-time (AUC) curve of pioglitazone 3.2 fold and prolonged its elimination half-life (T1/2) from 8.3 to 22.7 hours (P<0.001), but had no significant effect on its peak concentration (Cmax) compared with placebo (control). The Deng et al. study reported that gemfibrozil raised the mean total AUC of pioglitazone 3.4 fold and prolonged its T1/2 from 6.5 to 15.1 hours (P<0.001), but had no significant effect on Cmax. In regards to Pioglitazone and Rifampicin interaction, Jaakkola, et al 2006 reported that rifampicin caused a decrease in the plasma concentration of pioglitazone, probably by induction of CYP2C8. The Jaakkola publication showed that the potent CYP3A4 inhibitor itraconazole did not affect pioglitazone pharmacokinetics. Although the review of safety data did not provide any evidence of significant effects associated with interactions between pioglitazone and gemfibrozil and pioglitazone and rifampicin, there is a potential for interaction. Based on these data sections 4.4, 4.5 and 5.2 of the SPC have been updated to reflect the information regarding these reported drug interactions.
IB/0002	IB_10_Minor change in the manufacturing process of the active substance	08/11/2006	n/a		