



## Tandemact

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification <sup>1</sup> issued on	Commission Decision Issued <sup>2</sup> / amended on	Product Information affected <sup>3</sup>	Summary
IA/0069/G	This was an application for a group of variations.  A.7 - Administrative change - Deletion of manufacturing sites  B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	07/09/2023		SmPC, Labelling and PL	

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).



IB/0068	C.I.7.b - Deletion of - a strength	11/07/2023		SmPC, Labelling and PL	
PSUSA/2417/ 202107	Periodic Safety Update EU Single assessment - glimepiride / pioglitazone hydrochloride, metformin / pioglitazone, pioglitazone	10/03/2022	n/a		PRAC Recommendation - maintenance
T/0066	Transfer of Marketing Authorisation	03/06/2021	24/06/2021	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	24/06/2021	SmPC, Annex II, Labelling and PL	
IAIN/0064	B.III.1.a.1 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer	10/07/2020	n/a		
IA/0063	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	30/04/2020	n/a		

	manufacturer of a novel excipient				
WS/1680	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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 (EMA/H/C/PSUSA/00002417/201807) with regards to discontinuation of pioglitazone aRMMs.</p> <p>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</p>	28/11/2019	n/a		
IB/0062/G	<p>This was an application for a group of variations.</p> <p>B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings</p> <p>B.II.b.1.a - Replacement or addition of a</p>	07/11/2019	19/10/2020	SmPC, Annex II and PL	

<p>manufacturing site for the FP - Secondary packaging site</p> <p>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site</p> <p>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</p> <p>B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>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</p> <p>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms</p> <p>B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)</p> <p>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p>				
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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	27/05/2019	Annex II	Please refer to PSUSA-00002417-201807 EPAR:  Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
WS/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	27/05/2019	SmPC, Annex II, Labelling and PL	
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	14/12/2017	n/a		

	<p>Commission Regulation (EC) No 1234/2008.</p> <p>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation</p>				
WS/1138	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	11/05/2017	n/a		
PSUSA/2417/201607	<p>Periodic Safety Update EU Single assessment - glimepiride / pioglitazone hydrochloride, metformin / pioglitazone, pioglitazone</p>	09/03/2017	n/a		PRAC Recommendation - maintenance
IG/0766	<p>A.7 - Administrative change - Deletion of manufacturing sites</p>	02/02/2017	n/a		
WS/0991	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</p>	26/01/2017	n/a		<p>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</p>

					<p>Intervention after Stroke (IRIS) trial (IRIS Report) have also been provided.</p> <p>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.</p>
IG/0739/G	<p>This was an application for a group of variations.</p> <p>A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release</p> <p>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</p> <p>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</p> <p>B.III.1.a.2 - Submission of a new/updated or</p>	30/11/2016	10/11/2017	Annex II and PL	

	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		
R/0049	Renewal of the marketing authorisation.	21/07/2016	09/09/2016	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 Tandemact in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
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	09/09/2016	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

	<p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				significant increased risk.
WS/0875	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation</p>	01/04/2016	n/a		
WS/0827	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>C.I.13 - Other variations not specifically covered</p>	25/02/2016	n/a		n/a

	elsewhere in this Annex which involve the submission 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	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation</p>	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	20/11/2014	n/a		

	<p>Commission Regulation (EC) No 1234/2008.</p> <p>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).</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</p>				
WS/0647	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>The requested worksharing procedure proposed amendments to the Risk Management Plan (RMP).</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission</p>	20/11/2014	n/a		

	of studies to the competent authority				
WS/0609	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation</p>	25/09/2014	n/a		
WS/0541	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</p>	25/09/2014	n/a		N/A
IB/0037/G	<p>This was an application for a group of variations.</p> <p>A.1 - Administrative change - Change in the name and/or address of the MAH</p> <p>A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer</p>	23/07/2014	08/07/2015	SmPC, Annex II, Labelling and PL	

	responsible for batch release C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
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/0033	Periodic Safety Update	19/09/2013	13/11/2013	SmPC and PL	For further information please refer to: Tandemact-H-C-680-Grounds PSUV-33-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/0030	Transfer of Marketing Authorisation	25/03/2013	22/04/2013	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.	15/11/2012	14/01/2013	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.

	<p>This variation followed a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>				
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/0025/G	<p>This was an application for a group of variations.</p> <p>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site</p> <p>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site</p> <p>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site</p>	26/03/2012	n/a		
R/0023	Renewal of the marketing authorisation.	20/10/2011	02/03/2012	SmPC, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the

					<p>benefit risk profile of Tandemact continues to be favourable, but considers that its safety profile is to be closely monitored for the following reasons:</p> <p>The use of pioglitazone/glimepride is associated with a number of identified adverse events (cardiac failure, weight gain, macular oedema, hypoglycaemia, carcinogenicity in particular bladder cancer and bone fractures) as well as potential risks (hepatic events, 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. With regard to the identified risk of bladder cancer, 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. Therefore, the CHMP decided that the MAH should continue to submit 6- monthly PSURs and the MAH should, based on pharmacovigilance grounds, submit one additional renewal application in 5 years time.</p> <p>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. In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Portugal.</p>
A20/0022	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the	20/10/2011	22/12/2011		<p>Please refer to the CHMP Assessment Report: Revised Assessment Report for Actos, Glustin, Competact,</p>

	<p>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 authorisation should be maintained, varied, suspended or withdrawn.</p>				<p>Glubrava, Tandemact Article 20 procedures (EMA/H/C/0285/A-20/0046; EMA/H/C/0286/A-20/0044; EMA/H/C/0665/A-20/0030; EMA/H/C/0893/A-20/0015; EMA/H/C/0680/A-20/0022)</p>
IB/0021/G	<p>This was an application for a group of variations.</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>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</p>	01/09/2010	n/a		
II/0020	<p>Update of SPC and Labelling</p> <p>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</p>	18/02/2010	23/03/2010	SmPC and Labelling	<p>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</p>

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 and Labelling

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 tumorige
N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/09/2009	n/a	PL	
II/0018	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 DDPS (Pharmacovigilance)	23/07/2009	31/08/2009	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 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.
IB/0017	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	27/03/2009	n/a	SmPC	
IA/0016	IA_01_Change in the name and/or address of the marketing authorisation holder	23/02/2009	n/a	SmPC, Labelling and PL	
IB/0015	IB_17_a_Change in re-test period of the active substance	28/07/2008	n/a		
IB/0014	IB_17_a_Change in re-test period of the active substance	28/07/2008	n/a		
IB/0012	IB_25_a_01_Change to comply with Ph. -	28/07/2008	n/a		

	compliance with EU Ph. - active substance				
IA/0013	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	09/07/2008	n/a		
IA/0011	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	07/07/2008	n/a		
X/0006	<p>The new presentation consists in a new tablet strength (30 mg pioglitazone / 2 mg glimeperide). The active substances and the finished product are identical to the authorised strengths except for the strength. Relevant studies were submitted on bioequivalence and the influence of food. The available data supported this new strength application satisfactorily. No unknown safety issues arose during the assessment of this Annex II application for the line extension. The safety issues of pioglitazone and glimepiride apply to this 30mg/2mg pioglitazone/glimepiride strength. The product will be continuously followed in the future through the PSURs and the Follow-up measures agreed by the CHMP.</p> <p>Annex I_2.(c) Change or addition of a new strength/potency</p>	24/01/2008	31/03/2008	SmPC, Labelling and PL	
II/0010	Following a request from the CHMP, section 4.4 of Summary of Product Characteristics was updated in order to include a warning on the increased risk of haemolytic anaemia in patients with glucose-6-	18/10/2007	11/12/2007	SmPC and PL	The Pharmacovigilance Working Party (PhVWP) performed a review of drugs that might induce an increased risk of haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

	<p>phosphate dehydrogenase (G6PD) deficiency. The Package Leaflet was updated accordingly.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>				<p>Glibenclamide, a sulfonylurea agent, is known to be directly responsible for haemolytic anaemia in patients with G6PD deficiency. After the review of other sulphonylureas, the PhVWP was of the opinion that haemolytic anaemia in patients with G6PD deficiency is a class effect of sulfonylurea agents.</p> <p>The PhVWP and the CHMP considered that given a potential class effect, a warning statement should be added in the product information of all sulphonylurea agents. Therefore, the Marketing Authorisation Holder (MAH) for Tandemact was requested to submit this type II variation in order to include a warning regarding the increased risk of haemolytic anaemia in patients with G6PD deficiency taking glimepiride.</p>
II/0009	<p>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.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>	20/09/2007	30/11/2007	SmPC, Annex II and PL	<p>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.</p> <p>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.</p> <p>The main concern of the CHMP was the fact that both insulin and pioglitazone alone are associated with fluid</p>

					<p>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.</p> <p>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.</p>
II/0008	<p>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.</p> <p>Update of Summary of Product Characteristics</p>	20/09/2007	30/11/2007	SmPC	<p>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).</p> <p>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</p>

					<p>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 weight gain, oedema and heart failure were confirmed.</p> <p>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.</p> <p>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.</p>
II/0005	<p>The MAH applied for the replacement of the primary packaging from 30 tablets and 90 tablets HPDE bottles to 14, 28, 30, 50, 90 and 98 tablets in aluminium/aluminium blisters. The MAH will not market any longer the HPDE bottle presentations. As a consequence the MAH also applied for changes in the formulation, changes in the manufacturing process and tests methods of the finished product.</p> <p>New presentation(s)</p>	20/09/2007	12/11/2007	SmPC, Labelling and PL	
II/0004	<p>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.</p>	24/05/2007	27/08/2007	SmPC and PL	<p>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</p>

	Update of Summary of Product Characteristics and Package Leaflet			<p>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.</p> <p>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.</p> <p>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.</p> <p>The Package Leaflet was updated accordingly.</p>
IA/0007	IA_28_Change in any part of primary packaging material not in contact with finished product	15/06/2007	n/a	

	IA_36_b_Change in shape or dimensions of the container/closure - other pharm. forms				
IB/0003	IB_10_Minor change in the manufacturing process of the active substance	20/04/2007	n/a		
IB/0002	IB_10_Minor change in the manufacturing process of the active substance	20/04/2007	n/a		
IA/0001	IA_13_a_Change in test proc. for active substance - minor change	23/03/2007	n/a		