EMA/167731/2021

Glustin

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/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	06/06/2019	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 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 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		
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.
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 assessing bladder cancer risk with pioglitazone. The RMP has been updated accordingly. Furthermore, minor editorial changes were introduced in the PI. In	28/04/2016	28/04/2017	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.

	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				
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 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. Submission of the study AD-4833-411, a study on the utilization of pioglitazone in clinical practice in	20/11/2014	n/a		

	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.	25/09/2014	n/a		

	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
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/0060/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/06/2014	19/06/2015	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/0056	Periodic Safety Update	19/09/2013	13/11/2013	SmPC and PL	For further information please refer to: Glustin-H-C-286-Grounds PSUV-56-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		
IB/0055/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 B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	29/08/2013	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/0052	Transfer of Marketing Authorisation	28/03/2013	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	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.

	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				
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/0047/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	26/03/2012	n/a		
A20/0044	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)
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/07/2011	n/a	PL	
IB/0043/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 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	01/09/2010	n/a		
R/0042	Renewal of the marketing authorisation.	24/06/2010	31/08/2010	SmPC, Annex II, Labelling	

				and PL	
II/0041	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 and Labelling	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/0040	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	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.
IA/0038	IA_01_Change in the name and/or address of the marketing authorisation holder	23/02/2009	n/a	SmPC, Labelling and PL	
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/12/2008	n/a	PL	
IA/0036	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		
N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/06/2008	n/a	PL	

IA/0034	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	07/12/2007	n/a		
IB/0032	IB_10_Minor change in the manufacturing process of the active substance	20/09/2007	n/a		
IA/0033	IA_39_Change/addition of imprints, bossing or other markings	06/09/2007	n/a	SmPC and PL	
II/0026	Update of section 4.1 of the Summary of Products Characteristics to include the extension of indication of the use of pioglitazone in combination with insulin. Sections 4.2, 4.3, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics were updated consequently to reflect the new data, to reflect that pioglitazone is no more contraindicated with insulin treatment, and to add information on the risk of heart failure. Relevant sections of the Package Leaflet have been updated accordingly. Extension of Indication	19/07/2007	31/08/2007	SmPC and PL	Please refer to the scientific discussion: Glustin H-286-II-26-AR
II/0025	Update of section 4.1 of the Summary of Products Characteristics to extend the indication for the use of pioglitazone as triple oral therapy in combination with metformin and a sulphonylurea, in patients with insufficient glycaemic control despite dual oral therapy. Sections 4.4 and 4.8 have been consequently updated. The relevant sections of the Package Leaflet have been updated accordingly. Extension of Indication	19/07/2007	31/08/2007	SmPC and PL	Please refer to the scientific discussion: Glustin H-286-II-25-AR

II/0024	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 with regards to cardiovascular risk and sections 4.2 and 4.3 have been consequently amended. Section 4.1 has been re-organised without any change in the indications. Update of the Package Leaflet in accordance with the changes in the SPC and to include the full list of local representatives. Additionally, update of the Labelling to combine the different strengths and inclusion of information in Braille. Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/07/2007	31/08/2007	SmPC, Labelling and PL	At the time of the original Marketing Authorisation, 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.
II/0027	Update of the Summary of Product Characteristics	24/05/2007	20/08/2007	SmPC and PL	Further to the review of available information on increased

	(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				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/0031	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	10/07/2007	10/07/2007	SmPC, Labelling and PL	
IA/0030	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	10/07/2007	10/07/2007	SmPC, Labelling and PL	
II/0023	The Marketing Authorisation Holder referred to an update of sections 4.4, 4.5 and 5.2 of the Summary of Product Characteristics to include reference to potential interaction with gemfibrozil and with rifampicin. Update of Summary of Product Characteristics	21/09/2006	26/10/2006	SmPC	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. study demonstrated that gemfibrozil decreased the AUC(0-48) of M-III and M-IV by 42% and 45%, respectively. However, the total AUC(0-inf) values of these metabolites were not considered markedly reduced by gemfibrozil since elimination of these metabolites seemed to be considerably slower when administered with gemfibrozil. The Deng et al. study reported that no statistically significant changes were seen in the total AUC of M-III or M-IV after gemfibrozil pretreatment. Therefore, these metabolites do not seem to play a major role in this interaction between pioglitazone and gemfibrozil. In regards to Pioglitazone and Rifampicin interaction, Jaakkola, et al 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. A review of the MAH's global pioglitazone safety database shows no evidence that these interactions have given rise to any safety concern to date. The assessment of postmarketing reports in the Takeda and FDA safety databases did not suggest any clinical implications from the pharmacokinetic information shown in the 3 publications. However, there is a potential for interaction and it is possible that potential cases have not been considered up to now. Therefore SPC sections have been updated to reflect it. Section 4.4 Pioglitazone should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glycaemic control should be monitored closely. Pioglitazone dose adjustment within the recommended po
II/0020	This variation refers to an update of Sections 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable Effects) of the Summary of Product Characteristics in relation to cases of macular oedema associated with pioglitazone. The package leaflet (PL) has been updated accordingly. Annex II has been updated to reflect the Risk	01/06/2006	20/07/2006	SmPC, Annex II and PL	35 cases of macular oedema have been noted in post marketing reports in patients treated with pioglitazone. The information provided by these reports is limited although many cases appear to be associated with peripheral oedema. Most of the reports are from the United States in patients with more advanced disease. Concomitant insulin was used in 14 of 29 of these cases with no information in

	Management Plan. Update of Summary of Product Characteristics and Package Leaflet				6 cases. Pre-existing eye disease was noted in 18 cases with macular oedema in 6 cases, diabetic retinopathy in another 4 cases and no eye disease in one case. It is unclear whether or not there is a direct association between pioglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity and appropriate ophthalmologic referral should be considered. The SPC (sections 4.4 and 4.8) and the Package Leaflet (sections 2 and 4) has been updated to reflect this information.
IA/0022	IA_01_Change in the name and/or address of the marketing authorisation holder	17/05/2006	n/a	SmPC, Labelling and PL	
IA/0021	IA_01_Change in the name and/or address of the marketing authorisation holder	22/02/2006	n/a	SmPC, Labelling and PL	
IB/0018	IB_10_Minor change in the manufacturing process of the active substance	16/12/2005	n/a		
IA/0019	IA_13_a_Change in test proc. for active substance - minor change	14/11/2005	n/a		
IA/0017	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	14/11/2005	n/a		
R/0015	Renewal of the marketing authorisation.	27/07/2005	13/10/2005	SmPC, Annex II, Labelling and PL	

IA/0016	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	08/09/2005	08/09/2005	SmPC, Labelling and PL	
IB/0014	IB_33_Minor change in the manufacture of the finished product	18/03/2005	n/a		
II/0011	Update of section 5.1 of the SPC to include results of controlled pioglitazone clinical trials and data from a short term trial investigating the effects of pioglitazone treatment on postprandial lipid metabolism. The Marketing Authorisation Holder (MAH) also applied to remove the requirement for routine liver enzyme monitoring every two months during the first year of pioglitazone therapy in section 4.4 of the SPC. The Package Leaflet has been updated accordingly. In addition the MAH applied to delete the list of local representatives in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	18/11/2004	10/01/2005	SmPC and PL	The MAH applied for this variation to update section 5.1 of the SPC to take account of recently available results of controlled pioglitazone clinical trials, including two-year data from each of three clinical trials and data from a short term trial investigating the effects of pioglitazone treatment on postprandial lipid metabolism. The Marketing Authorisation Holder (MAH) also applied to remove the requirement for routine liver enzyme monitoring every two months during the first year of pioglitazone therapy in section 4.4 of the SPC based on clinical trial and post-marketing data. The CHMP agreed that there is an acceptable benefit/risk for lifting the requirement for periodic on-therapy LFT monitoring with pioglitazone. In order to better follow the effects in the market situation of this amendment the MAH is requested to provide yearly reports on hepato-biliary adverse reactions. The Package Leaflet has been updated accordingly. In addition the MAH applied to delete the list of local representatives in the Package Leaflet.
IA/0013	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	11/11/2004	n/a		

IA/0012	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	20/10/2004	n/a		
X/0010	X-3-iii_Addition of new strength	26/06/2003	16/09/2003	SmPC, Labelling and PL	
II/0009	Extension of Indication	22/05/2003	28/08/2003	SmPC, Annex II and PL	
II/0008	Extension of Indication	22/05/2003	28/08/2003	SmPC and PL	
II/0006	Update of Summary of Product Characteristics	21/11/2002	17/03/2003	SmPC and Annex II	
I/0007	11_Change in or addition of manufacturer(s) of active substance 12_Minor change of manufacturing process of the active substance 24_Change in test procedure of active substance	11/12/2002	16/12/2002		
II/0005	Update of Summary of Product Characteristics	13/12/2001	12/04/2002	SmPC	
I/0004	11_Change in or addition of manufacturer(s) of active substance 12_Minor change of manufacturing process of the active substance 24_Change in test procedure of active substance	06/04/2001	n/a		
I/0003	30_Change in pack size for a medicinal product	12/12/2000	31/12/2000	SmPC, Labelling and	

				PL	
I/0002	12_Minor change of manufacturing process of the active substance 11b_Change in supplier of an intermediate compound used in manufacture of the active substance 12a_Change in specification of starting material/intermediate used in manuf. of the active substance	04/12/2000	n/a		
I/0001	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	15/11/2000	n/a		