EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Avandamet

Procedural steps taken and scientific information after the authorisation

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
A20/0063	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 8 July 2010, the opinion of the CHMP on measures necessary to ensure the safe use of the above mentioned medicinal product further to the CHMP review on the cardiovascular safety of rosiglitazone-containing medicinal products and its impact on the benefit-risk balance following new information suggesting an increase in the risk of cardiovascular outcomes with rosiglitazone-containing medicinal products.	22/09/2010	03/12/2010		Please refer to the Assessment Report: Avandamet-H-522-A20-63-Assessment Report-Article 20
II/0059	Update of sections 4.4, 4.8 and 5.1 of the Summary of Product Characteristics to reflect the results of the RECORD study and to include	18/02/2010	26/03/2010	SPC, Annex II, PL	Update of sections 4.4, 4.8 and 5.1 of the Summary of Product Characteristics to reflect the results of the RECORD study and to include cardiac safety data from an update of the meta-analysis of 42 short term studies:

[1] Notifications are issued for type I variations (unless part of a group or a worksharing application). Opinions are issued for all other procedures.
[2] No Commission Decision is issued for type IA and type IB variations or for type II variations and annual re-assessments that do not affect the annexes.
[3] SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	cardiac safety data from an update of the meta-analysis of 42 short term studies investigating cardiac ischaemia. An updated Risk Management Plan (RMP) was submitted as part of this variation. The Annex II has been updated to reflect the new version number of the RMP. The Package leaflet has been updated to include minor corrections and to update the contact details of the local representatives. Update of Summary of Product Characteristics and Package Leaflet				- The RECORD trial was a large (4,447 subjects), open-label, prospective, controlled study (mean follow-up 5.5 years) in which patients with type 2 diabetes inadequately controlled with metformin or sulphonylurea were randomised to add-on rosiglitazone or metformin or sulphonylurea. The mean duration of diabetes in these patients was approximately 7 years. The adjudicated primary endpoint was cardiovascular hospitalisation (which included hospitalisations for heart failure) or cardiovascular death. No difference in the number of adjudicated primary endpoint events for rosiglitazone (321/2220) versus active control (323/2227) (HR 0.99, CI 0.85-1.16) was observed, meeting the pre-defined non-inferiority criterion of 1.20 (non-inferiority p = 0.02). HR and CI for key secondary endpoints were: all-cause death (HR 0.86, CI 0.68-1.08), MACE (Major Adverse Cardiac Events - cardiovascular death, acute myocardial infarction, stroke) (HR 0.93, CI 0.74-1.15), cardiovascular death (HR 0.84, CI 0.59-1.18), acute myocardial infarction (HR 1.14, CI 0.80-1.63) and stroke (HR 0.72, CI 0.49-1.06). In a sub-study at 18 months, add-on rosiglitazone dual therapy was non-inferior to the combination of sulphonylurea plus metformin for lowering HbA1c. In the final analysis at 5 years, an adjusted mean reduction from baseline in HbA1c of 0.14% for patients on rosiglitazone added to metformin versus an increase of 0.17% for patients taking sulphonylurea added to metformin was seen during treatment with randomised dual-combination therapy (p<0.0001 for treatment difference). An adjusted mean reduction in HbA1c of 0.24% was seen for patients taking rosiglitazone added to sulphonylurea, versus a reduction in HbA1c of 0.10% for patients taking metformin added to sulphonylurea, (p=0.0083 for treatment difference). There was a significant increase in

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					heart failure (fatal and non-fatal) (HR 2.10, CI 1.35-3.27) and bone fractures (Risk Ratio 1.57, CI 1.26-1.97) in rosiglitazone-containing treatments compared to active control (see sections 4.4 and 4.8). A total of 564 patients withdrew from cardiovascular follow-up, which accounted for 12.3% of rosiglitazone patients and 13% of control patients; representing 7.2% of patient-years lost for cardiovascular events follow-up and 2.0% of patient-years lost for all cause mortality follow-up. - In an update to the retrospective analysis of 42 pooled short-term clinical studies, including 10 further studies that met the criteria for inclusion, but were not available at the time of the original analysis, the overall incidence of events typically associated with cardiac ischaemia was not statistically different for rosiglitazone containing regimens, 2.21% versus combined active and placebo comparators, 2.08% [HR 1.098 (95% CI 0.809 - 1.354)]. In a prospective cardiovascular outcomes study (mean follow-up 5.5 years) the primary endpoint events of cardiovascular death or hospitalisation were similar between rosiglitazone and active comparators [HR 0.99 (95% CI 0.85 - 1.16)]
II/0060	Update of the Detailed Description of the Pharmacovigilance System (DDPS) including change of the Qualified Person for Pharmacovigilance (QPPV). Annex II has been updated with the new version number. Update of DDPS (Pharmacovigilance)	17/12/2009	20/01/2010	Annex II	The DDPS has been updated (version 7.2) to reflect the change of the QPPV as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements.

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IA/0062	01_Change in the name and/or address of the marketing authorisation holder	15/12/2009	n/a	SPC, Labelling, PL	
IB/0061	33_Minor change in the manufacture of the finished product	02/12/2009	n/a		
II/0057	Update of the Product Information to include data from a completed clinical study (ADOPT). Sections 4.2 and 5.1 of the Summary of Product Characteristics (SPC) have been updated to reflect the study findings. Section 4.8 of the SPC has also been updated with revised numbers for the incidence of myocardial ischaemia from the Integrated Clinical Trial (ICT) analysis. Other minor administrative corrections have been made to the Labelling and the Package Leaflet including an update of the details of the local representatives. Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/07/2009	25/08/2009	SPC, Labelling, PL	The following new text was added to section 5.1 of the SPC (Pharmacodynamic Properties): [...ADOPT (A Diabetes Outcome Progression Trial) was a multicentre, double-blind, controlled trial with a treatment duration of 4-6 years (median duration of 4 years), in which rosiglitazone at doses of 4 to 8 mg/day was compared to metformin (500 mg to 2000 mg/day) and glibenclamide (2.5 to 15 mg/day) in 4351 drug naive subjects recently diagnosed (?3 years) with type 2 diabetes. Rosiglitazone treatment significantly reduced the risk of reaching monotherapy failure (FPG>10.0 mmol/L) by 63% relative to glibenclamide (HR 0.37, CI 0.30-0.45) and by 32% relative to metformin (HR 0.68, CI 0.55-0.85) during the course of the study (up to 72 months of treatment). This translates to a cumulative incidence of treatment failure of 10.3% for rosiglitazone, 14.8% for metformin and 23.3% for glibenclamide treated patients. Overall, 43%, 47% and 42% of subjects in the rosiglitazone, glibenclamide and metformin groups respectively withdrew due to reasons other than monotherapy failure. The impact of these findings on disease progression or on microvascular or macrovascular outcomes has not been determined (see section 4.8). In this study, the adverse events observed were consistent with the known adverse event profile for each of the treatments, including continuing weight gain with

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					rosiglitazone. An additional observation of an increased incidence of bone fractures was seen in women with rosiglitazone (see sections 4.4 and 4.8)….] The CHMP considered that the high withdrawal rate in the ADOPT was a drawback of the study, and it cannot be completely excluded that this does not affect the robustness of the results, even though the sensitivity analyses presented by the MAH could be considered as supportive. However, considering the paucity of long-term comparative data for medicinal products used in the treatment of Type 2 Diabetes Mellitus, inclusion in the product information of the above text with information deriving from the ADOPT study was considered acceptable by the CHMP.
II/0058	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Annex II has been updated to reflect the new version number of the DDPS. Update of DDPS (Pharmacovigilance)	23/07/2009	25/08/2009	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/0056	38_c_Change in test procedure of finished product - other changes	04/03/2009	n/a		
IB/0055	42_a_01_Change in shelf-life of finished product - as packaged for sale	07/11/2008	n/a	SPC	
IA/0054	13_a_Change in test proc. for active substance - minor change	30/09/2008	n/a		

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IB/0050	33_Minor change in the manufacture of the finished product	13/08/2008	n/a		
R/0048	Renewal of the Marketing Authorisation.	30/05/2008	08/08/2008	SPC, Annex II, Labelling, PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of AVANDAMET continues to be favourable but considers that its safety profile is to be closely monitored for the following reasons: The cardiac safety of rosiglitazone is a major concern. Currently, no definite conclusion can be drawn on the risk of cardiac ischemia (both Congestive Heart Failure and Myocardial ischaemia). More data are needed, among which the results of the RECORD-study, to draw a conclusion on the cardiac safety and the related clinical implications. Furthermore the risk of bone fractures remains another source of concern. Because of the uncertainties concerning the cardiovascular safety and the risk of bone fractures of rosiglitazone, the benefit-risk balance of AVANDAMET should be re-evaluated on a regular basis in PSURs or when new relevant information becomes available. The MAH should submit one yearly PSURs. Therefore, based upon the safety profile of AVANDAMET, which requires the submission of 1-yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
IB/0053	17_b_Change in the storage conditions for the active substance	30/07/2008	n/a		
IB/0052	14_b_Change in manuf. of active	02/07/2008	n/a		

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	substance without Ph. Eur. certificate - new manufacturer				
IB/0051	14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	02/07/2008	n/a		
IA/0049	05_Change in the name and/or address of a manufacturer of the finished product	19/03/2008	n/a		
II/0046	Update of Summary of Product Characteristics Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) to include the possible risk of ischaemic heart disease during rosiglitazone treatment further to the Benefit-Risk assessment (FUM 022). Also update of section 4.3 of the SPC to include a contra-indication for the use of rosiglitazone in patients with an Acute Coronary Syndrome and a related warning in section 4.4 of the SPC. In addition section 4.4 of the SPC has been updated to strengthen the wording regarding the concomitant use of rosiglitazone and insulin. Update of Summary of Product Characteristics	24/01/2008	03/03/2008	SPC	The CHMP finalised the re-assessment of the benefits and risks of rosiglitazone in October 2007, concluding that the benefits of rosiglitazone continued to outweigh their risks in their approved indications, but that the product information for rosiglitazone should be changed. This variation is a follow-up measure to this benefit-risk re-assessment. In this variation a new warning has been included in section 4.4 of the SPC stating that treatment with rosiglitazone may be associated with an increased risk of myocardial ischaemic events and that the use of rosiglitazone in patients with ischemic heart disease and/or peripheral arterial disease is not recommended. Additionally section 4.8 of the SPC has been updated. Also a new contra-indication have been added in section 4.3 of the SPC stating that rosiglitazone must not be used in patients with an acute coronary syndrome, because this medicine has not been studied in controlled trials in this specific patient group. Additionally section 4.4 has been updated. Section 4.4 of the SPC has also been updated to strengthen the wording regarding the concomitant use of rosiglitazone and insulin.
IA/0047	15_a_Submission of Ph. Eur.	06/02/2008	n/a		

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	certificate for active substance - approved manufacturer				
IA/0045	11_a_Change in batch size of active substance or intermediate - up to 10-fold	08/11/2007	n/a		
IA/0043	09_Deletion of manufacturing site	08/10/2007	n/a		
IA/0044	05_Change in the name and/or address of a manufacturer of the finished product	08/10/2007	n/a		
IB/0042	33_Minor change in the manufacture of the finished product	19/09/2007	n/a		
IB/0040	33_Minor change in the manufacture of the finished product	25/06/2007	n/a		
IB/0039	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	22/06/2007	n/a		
IB/0041	31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits, 33_Minor change in the manufacture of the finished product	22/06/2007	n/a		
II/0036	Update of Section 4.4 and Section 4.8 of the SPC to inform prescribers about new safety information concerning bone fractures following analysis of a long term efficacy and safety study (Study ADOPT). The corresponding sections of the Patient Leaflet have been	26/04/2007	04/06/2007	SPC, PL	The results of a randomised, double-blind, parallel group study (ADOPT) of 4,360 patients with recently diagnosed type 2 diabetes mellitus whose progression of diabetes was followed for 4-6 years were recently published (Kahn et al., 2006). Data showed that more female patients who received rosiglitazone experienced fractures (mainly of the upper arm, hand and foot) than did female patients who received either metformin or glibenclamide.

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	appropriately revised. Update of Summary of Product Characteristics and Package Leaflet				The observed incidence of fractures for male patients in ADOPT was similar among the treatment groups. Wording has been included in sections 4.4 and 4.8 of the SPC for rosiglitazone-containing products to reflect this new information, with update to the relevant sections of the Package Leaflet.
IA/0037	15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	29/05/2007	n/a		
IA/0038	32_b_Change in batch size of the finished product - downscaling down to 10-fold	29/05/2007	n/a		
II/0023	This variation refers to the deletion of the contra-indication to use AVANDAMET in combination with insulin. As a consequence sections 4.3, 4.4 and 4.8 of the Summary of Product Characteristics have been updated. The Package Leaflet (PL) has been updated accordingly. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to include the details of the Bulgarian and Romanian local representatives in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	24/01/2007	SPC, PL	In support of this type II variation the MAH submitted AVANDAMET (AVM) study 009, in which insulin was added to established AVM therapy. This study was discussed in conjunction with the data of 6 other studies evaluating the effects of rosiglitazone on glycaemic control in patients with type 2 diabetes who were inadequately controlled on insulin therapy. Study 009 was the pivotal study. It was a 24 week study where insulin was added to the AVANDAMET, therapyand insulin study (24 weeks) the addition of insulin to AVANDAMET therapy treatment resulted in a decrease from baseline in mean HbA1c of 1.96% compared to a decrease of 1.32% in the insulin monotherapy group (mean treatment difference: 0.65%; p<0.0001). The study design included patients up to the age of 70 and allowed the screening out of The study design excluded patients older than 70 years and subjects who were sensitive to fluid related adverse effects by excluding subjectsthose who developed oedema or whose oedema worsened during the first 8 weeks after initiating

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					AVANDAMET therapy prior to addition of insulin. In addition, the mean final total daily insulin dose was lower in the AVANDAMET plus insulin group (33.2U vs. 58.6U, mean treatment difference: 25.4U, p<0.0001). Althoughthe number of subjects reporting hypoglycaemia was similar between AVANDAMET plus insulin and the insulin monotherapy groups., tThe number of hypoglycaemic events was higher in the AVANDAMET plus insulin group compared to the insulin monotherapy group (535 vs. 365). Although oOedema occurred more frequently in subjects taking AVANDAMET plus insulin compared with insulin monotherapy (7.0% vs. 3.0%) (7.0% vs. 3.0%), no events of heart failure were reported with either treatment regimen. In view of the available data the CHMP concluded that the data are adequate to support the deletion of the contraindication with insulin however they expressed their concerns regarding the risk of fluid retention and heart failure. Therefore the product information has been amended to reflect the risk for increased fluid retention and heart failure when receiving AVM in combination with insulin. Increased monitoring of patients is recommended. Also the increased risk for oedema and hypoglycymia are reflected in the SPC. Sections 4.3, 4.4 and 4.8 of the SPC have been updated. The Package Leaflet has been updated accordingly.
II/0034	This variation refers to update sections 4.2, 5.1 and 5.2 of the Summary of Product Characteristics to reflect the paediatric experience with rosiglitazone derived from an active controlled clinical trial (rosiglitazone up to 8 mg daily or	18/10/2006	22/11/2006	SPC	The results of the peadiatric study showed that improvement in HbA1c from baseline achieved statistical significance only in the metformin group. Rosiglitazone failed to demonstrate non-inferiority to metformin. Following rosiglitazone treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus.

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	metformin up to 2,000 mg daily) of 24 weeks duration performed in 197 children (10-17 years of age) with type 2 diabetes. Update of Summary of Product Characteristics				A population pharmacokinetic analysis including 96 paediatric patients aged 10 to 18 years and weighing 35 to 178 kg suggested similar mean CL/F in children and adults. Individual CL/F in the paediatric population was in the same range as individual adult data. CL/F seemed to be independent of age, but increased with weight in the paediatric population. The available data do not support efficacy in the paediatric population and therefore such use is not recommended. Sections 4.2, 5.1 and 5.2 of the SPC have been updated to reflect this information.
II/0032	The Marketing Authorisation Holder applied for an update of section 4.8 of the Summary of Product Characteristics to add the skin reactions 'pruritis' and 'rash' and the event 'anaphylactic reaction'. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	22/11/2006	SPC, PL	The MAH applied for this variation to include information regarding skin reactions (pruritis and rash) and anaphylactic reaction in section 4.8 of the SPC, and related changes in the Package Leaflet. In the post-marketing data review, 25 pivotal reports were identified of which, 12 reported pruritis, 16 reported rash/drug eruption, 4 described urticaria, and 3 described anaphylactic reaction/Type III immune complex reaction. These 25 pivotal reports were evaluated based on the criteria for diagnosis of a drug reaction. Nine of the 25 reports described the time to onset to be 3 days or less. Three additional reports described the time to onset to be 9 to 21 days. All 25 of these pivotal reports described a positive rechallenge. After review of the post-marketing data, seven reports of anaphylactic reaction were identified. All of these seven reports were from spontaneous sources, one of which was a consumer report. Four of these seven reports described the onset of the anaphylactic reaction to be within two days following the start of therapy. The

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					remaining three reports described the onset as 21 days, 19 months and several weeks. Six of the seven reports were serious and one was considered non-serious. None of these seven reports described a fatal outcome. Two of the seven anaphylactic events described a positive rechallenge during RSG use.
II/0033	Update of section 4.8 of the Summary of Product Characteristics in order to reflect information regarding congestive heart failure. Update of Summary of Product Characteristics	18/10/2006	22/11/2006	SPC	The MAH presented the results of a placebo-controlled one-year trial in patients with congestive heart failure NYHA class I-II, showing that a worsening or possible worsening of heart failure occurred in 6.4% of patients treated with rosiglitazone, compared with 3.5% on placebo. Section 4.8 of the SPC was updated with this information.
II/0031	Update of sections 4.2, 4.4 and 4.8 of the Summary of Product Characteristics (SPC) to include information on cardiovascular events following a comprehensive review of data from clinical trials and an epidemiological study. The relevant sections 2 and 4 of the Package Leaflet (PL) have been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	24/10/2006	SPC, PL	The Marketing Authorisation Holder (MAH) applied in this type II variation for the update of the sections 4.2, 4.4, 4.8 of the SPC, and related sections of the PL, following analysis of cardiovascular events using an integrated dataset of 42 rosiglitazone clinical trials, and data from an epidemiological study that evaluated the relative risk of myocardial infarction and coronary revascularization in adults with type 2 diabetes initiating rosiglitazone in clinical practice. The MAH has provided new data concerning the risk for congestive heart failure in patients treated with rosiglitazone, especially in combination with a sulphonylurea or insulin. The results also indicate that there could be a risk for ischaemic cardiac events. Even if epidemiological data do not support this, the CHMP concluded that this particular risk can not be ruled out. As a consequence the MAH wished to update the SPC with information regarding these risks. Sections 4.2, 4.4, 4.8 of the SPC and 2, 4 of the PL have been updated.
II/0030	Update of the section 4.6 of the Summary of Product Characteristics,	21/09/2006	24/10/2006	SPC	The Marketing Authorisation Holder (MAH) applied in this type II variation for the update of section 4.6 of the SPC

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	following the publication of literature which concluded that rosiglitazone crosses the placenta in the first trimester of human pregnancy. Update of Summary of Product Characteristics				in line with published literature that concluded that rosiglitazone crosses the placenta in the first trimester of human pregnancy. In that respect the following statement was added in the section 4.6 of the SPC (Rosiglitazone has been reported to cross the human placenta and to be detectable in foetal tissues).
IB/0035	10_Minor change in the manufacturing process of the active substance	18/10/2006	n/a		
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/08/2006	n/a	Labelling, PL	
II/0022	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 (SPC) in relation to cases of macular oedema reported in patients treated with thiazolidinediones including rosiglitazone. The package leaflet (PL) has been updated accordingly. Update of Summary of Product Characteristics, Labelling and Package Leaflet	01/06/2006	20/07/2006	SPC, Labelling, PL	The MAH received 29 reports of new onset and worsening macular oedema in patients treated with rosiglitazone. 22 reports were identified as key reports. 20 of which were received from the United States. Of these 22 key cases, the majority reported concurrent peripheral oedema. In about half of the cases, macular oedema developed within 3 months of initiation or uptitration of rosiglitazone treatment. In ten cases, rosiglitazone was used concurrently with insulin, which is a contraindicated combination in the EU. The majority of cases had a history of risk factors of macular oedema. In some cases, the macular oedema resolved or improved following discontinuation of therapy and in one case macular oedema resolved after dose reduction. It is unclear whether or not there is a direct association between rosiglitazone 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

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					2 and 4) has been updated to reflect this information.
IB/0028	31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits	27/06/2006	n/a		
IB/0029	31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits	27/06/2006	n/a		
IA/0027	31_a_Change to in-process tests/limits during manufacture - tightening of in-process limits	09/06/2006	n/a		
II/0021	Update of section 4.8 (Undesirable Effects) of the Summary of Product Characteristics (SPC) and relevant sections of the Package Leaflet (PL). Update of Summary of Product Characteristics, Labelling and Package Leaflet	27/04/2006	02/06/2006	SPC, Annex II, Labelling, PL	The MAH applied for this type II variation to reflect the interaction between metformin (MET) and cationic drugs (e.g. cimetidine) in the SPC and Package Leaflet based on the results of a study conducted by Somogyi et al investigating the potential for interaction between MET and a cationic drug cimetidine. This study conducted in seven normal healthy volunteers showed that cimetidine administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and Cmax by 81%. This drug-drug interaction is due to the inhibition by cimetidine of the renal tubular secretion of MET, resulting in higher circulating MET plasma concentrations. Therefore close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic drugs that are eliminated by renal tubular secretion are co-administered. Sections 4.4 and 4.5 of the SPC and section 2 of the Package Leaflet have been updated to reflect this interaction.
IA/0025	07_a_Replacement/add. of	18/04/2006	n/a		

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	manufacturing site: Secondary packaging site				
IA/0024	36_ b_Change in shape or dimensions of the container/closure - other pharm. forms	09/03/2006	n/a		
II/0018	Update of Summary of Product Characteristics and Package Leaflet	14/12/2005	30/01/2006	SPC, PL	The MAH applied for this type II variation to reflect the interaction between metformin and cationic drugs (e.g. cimetidine) in the SPC and Package Leaflet based on the results of a study conducted by Somogyi et al investigating the potential for interaction between MET and a cationic drug cimetidine. This study conducted in seven normal healthy volunteers showed that cimetidine administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and Cmax by 81%. This drug-drug interaction is due to the inhibition by cimetidine of the renal tubular secretion of MET, resulting in higher circulating MET plasma concentrations. Therefore close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic drugs that are eliminated by renal tubular secretion are co-administered. Sections 4.4 and 4.5 of the SPC and section 2 of the Package Leaflet have been updated to reflect this interaction.
IB/0019	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	16/11/2005	16/11/2005	SPC, Labelling, PL	
IB/0020	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	16/11/2005	16/11/2005	SPC, Labelling, PL	
II/0017	Extension of indication to add a triple	13/10/2005	15/11/2005	SPC, PL	Please refer to Scientific Discussion: Avandamet-H-522-

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	oral combination indication for AVANDAMET with a sulphonylurea (SU), based on data from clinical studies. Several sections of the Summary of Product Characteristics (SPC) and Package Leaflet (PL) have been updated to reflect the new safety information including an update of section 5.1 of the SPC to reflect 18-month interim data from a long term ongoing trial for rosiglitazone. In addition the MAH applied to include some minor linguistic changes in section 5.2 of the SPC. Extension of Indication				II-17
II/0012	Change(s) to the manufacturing process for the active substance	21/04/2005	28/04/2005		
IA/0016	32_b_Change in batch size of the finished product - downscaling down to 10-fold	24/02/2005	n/a		
IB/0015	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	24/02/2005	n/a		
IB/0014	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	01/02/2005	01/02/2005	SPC, Labelling, PL	
II/0008	Update of sections 4.4 and 4.5 of the	18/11/2004	20/01/2005	SPC, PL	The lipid lowering agent gemfibrozil has previously been

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	Summary of Product Characteristics (SPC) to include data relating to interactions between rosiglitazone and gemfibrozil and to reflect the reported drug interaction between rosiglitazone and rifampicin. The Package Leaflet has been updated accordingly. In addition the Marketing Authorisation Holder applied to update the contact details of the Estonian local representative in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet				shown to reduce the clearance of substrates metabolised by CYP2C9, 2C19, 1A2, 2C8, and UGT 1A1 and/or 1A3 (Preuksaritanont, 2002). In August 2003, the literature featured a single-dose rosiglitazone and a repeat-dose gemfibrozil pharmacokinetic (PK) study (Niemi, 2003), which was conducted in 10 healthy volunteers. Gemfibrozil increased the mean area under the plasma rosiglitazone concentration-time curve (AUC) 2.3-fold (range 1.5- to 2.8-fold); and prolonged the elimination half-life (t½) of rosiglitazone from 3.6 to 7.6 hours. The peak plasma rosiglitazone concentration (Cmax) was increased only 1.2-fold (range 0.9- to 1.6-fold). Following this publication, the MAH also performed a study to investigate the interaction between gemfibrozil and rosiglitazone (BRL-049653/902). The MAH applied for this type II variation to update sections 4.4 and 4.5 of the SPC to reflect the interaction data from the publication and MAH's study. A publication (Park, 2004) reported a 65% decrease in the AUC for rosiglitazone when co-administered with rifampicin, an inducer of CYP2C8 and the intestinal and hepatic CYP enzyme system (Finch 2002). The MAH applied for this type II variation to incorporate the findings of this study in the SPC (sections 4.4 and 4.5) to provide recommendations on concomitant use of rosiglitazone with CYP inducers. The Package Leaflet has been updated accordingly to reflect this information.
II/0010	The Marketing Authorisation Holder applied to remove the requirement for routine liver enzyme monitoring every two months during the first year of rosiglitazone therapy in section 4.4 of the Summary of	18/11/2004	20/01/2005	SPC, PL	The MAH applied to remove the requirement for routine liver enzyme monitoring every two months during the first year of rosiglitazone 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

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	Product Characteristics based on clinical trial and post-marketing data. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				(liver function test) monitoring with rosiglitazone. In order to better follow the effects in the market situation of this amendment the MAH was requested to provide all reports of hepato-biliary adverse reactions, especially hepatitis and acute liver failure. These reports will be submitted within the AVANDAMET PSURs. The Package Lealfet has been updated accordingly.
IA/0013	07_a_Replacement/add. of manufacturing site: Secondary packaging site	25/10/2004	n/a		
IA/0011	07_a_Replacement/add. of manufacturing site: Secondary packaging site	11/10/2004	n/a		
X/0001	Addition of new strength - 2 mg/1000mg. 02_iii_Change or addition of a new strength/potency	03/06/2004	02/09/2004	SPC, Labelling, PL	The new presentations consists in one new tablet strength (2 mg rosiglitazone/1000 mg metformin hydrochloride). Pack sizes are: 14, 28 and 36 film coated tablets. Except for the limited number of points, which can be addresed as part of the post authorisation commitments, the quality of this new strength is considered to be acceptable when used in accordance with the conditions in the SPC. The application is supported by a single pharmacokinetic study, which serves to bridge the new tablet strength to the clinical safety and efficacy established in the original strengths authorised in Avandamet marketing authorisation.
X/0002	Addition of new strength - 4 mg/1000 mg. 02_iii_Change or addition of a new strength/potency	03/06/2004	02/09/2004	SPC, Labelling, PL	The new presentations consists in one new tablet strength (4 mg rosiglitazone/1000 mg metformin hydrochloride). Pack sizes are: 14, 28 and 36 film coated tablets. Except for the limited number of points, which can be addresed as part of the post authorisation

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					commitments, the quality of this new strength is considered to be acceptable when used in accordance with the conditions in the SPC. The application is supported by a single pharmacokinetic study, which serves to bridge the new tablet strength to the clinical safety and efficacy established in the original strengths authorised in Avandamet marketing authorisation.
II/0006	Update of Summary of Product Characteristics and Package Leaflet Update of Summary of Product Characteristics and Package Leaflet	03/06/2004	13/07/2004	SPC, Labelling, PL	Update to bring Product Information in accordance with the QRD templates, CHMP Note for Guidance on Declaration of Storage Conditions, Guideline on the Excipients in the Label and Package Leaflet of Medicinal products for Human Use. To keep the labelling of the currently approved presentations for Avandamet in line with the labelling information for the new strengths, the sentence "Read the package leaflet before use" has been moved from section 7 "other special warnings if necessary" on the outer carton (labelling) to section 5 "method and routes of administration.
IA/0009	15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	05/07/2004	n/a		
N/0007	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/05/2004	n/a	PL	
IB/0004	33_Minor change in the manufacture of the finished product	23/03/2004	n/a		
IB/0005	33_Minor change in the manufacture of the finished product	23/03/2004	n/a		
IA/0003	06_a_Change in ATC code: Medicinal products for human use	04/03/2004	n/a	SPC	