EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Avandia

Procedural steps taken and scientific information after the authorisation

Changes made after 1 September 2003

For procedures finalised before 1 September 2003, please refer to 'Procedural steps taken until cut-off date

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
A20/0075	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: Avandia-H-268-A20-75-Assessment Report-Article 20

[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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R/0074	Renewal of the marketing authorisation	18/03/2010	26/05/2010	SPC, 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 AVANDIA continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of this medicinal product continues to be favourable but considers that its safety profile is to be closely monitored for the following reasons: The use of rosiglitazone is associated with a number of identified adverse events (PPARγ fluid retention including heart failure, weight gain, anaemia, macular oedema, and bone fractures) as well as potential risks (hepatic events, cardiac ischemia in short-term treatment, long-term cardiovascular outcomes, clinical effect of lipid changes, and carcinogenicity) to be closely monitored and to be reported in yearly PSURs and included in the Risk Management Plan. Results from several studies are also awaited to provide further answers on the risk of bone fractures and cardiovascular safety. Therefore, based upon the safety profile of AVANDIA, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should, on the basis of pharmacovigilance grounds, submit one additional renewal application in 5 years time.
II/0071	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.4, 4.8 and 5.1	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

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	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 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.				studies: - 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

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					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 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. - The MAH also submitted 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/0072	Update of DDPS (Pharmacovigilance) Update of the Detailed Description of	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

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	the Pharmacovigilance System (DDPS) including change of the Qualified Person for Pharmacovigilance (QPPV). Annex II has been updated to reflect the new version number.				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.
IA/0073	01_Change in the name and/or address of the marketing authorisation holder To change the name of the Marketing Authorisation Holder	24/11/2009	n/a	SPC, Labelling, PL	
II/0070	Update of DDPS (Pharmacovigilance) Update of the Detailed Description of the Pharmacovigilance System (DDPS). Annex II has been updated to reflect the new version number of the DDPS.	23/07/2009	21/08/2009	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.
II/0068	Update of Summary of Product Characteristics, Labelling and	23/04/2009	28/05/2009	SPC, Annex II, Labelling,	The following new text was added to section 5.1 of the SPC (Pharmacodynamic Properties):

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	Package Leaflet 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.			PL	[... 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 naïve 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).

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					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 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.
IB/0069	33_Minor change in the manufacture of the finished product	06/05/2009	n/a		
IA/0067	13_a_Change in test proc. for active	30/09/2008	n/a		

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	substance - minor change				
N/0066	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/09/2008	n/a	PL	
IB/0064	14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	27/08/2008	n/a		
IB/0065	14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	15/07/2008	n/a		
IB/0062	26_a_Change in the specification of immediate packaging - tightening of specification limits	20/05/2008	n/a		
IA/0061	07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms, 08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing, 07_a_Replacement/add. of manufacturing site: Secondary	07/05/2008	n/a	Annex II, PL	

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	packaging site				
IA/0060	05_Change in the name and/or address of a manufacturer of the finished product	05/05/2008	n/a		
IA/0063	36_ b_Change in shape or dimensions of the container/closure - other pharm. forms	05/05/2008	n/a		
IB/0059	31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits	21/04/2008	n/a		
II/0057	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 029). 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	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

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	SPC.				section 4.8 of the SPC has been updated. Also a new contra-indication has 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.
IB/0058	33_Minor change in the manufacture of the finished product	30/01/2008	n/a		
II/0052	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.3 of the Summary of Products Characteristics (SPC) in order to remove the contra-indication for the use of Avandia in combination with insulin. Consequently a contra-indication with diabetic ketoacidosis or diabetic pre-coma was added to the same section. Additionally, section 4.4 of the SPC has been updated with warnings regarding the risks of the use of rosiglitazone in combination with insulin. The Package Leaflet	18/10/2007	21/11/2007	SPC, PL	Please refer to the scientific discussion: Avandia-H-C-268-II-52 scientific discussion

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	has been amended accordingly.				
IA/0056	11_a_Change in batch size of active substance or intermediate - up to 10-fold	14/11/2007	n/a		
IA/0055	05_Change in the name and/or address of a manufacturer of the finished product	05/10/2007	n/a		
IA/0054	09_Deletion of manufacturing site	05/10/2007	n/a		
II/0053	Update of Summary of Product Characteristics and Package Leaflet 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 appropriately revised.	26/04/2007	30/05/2007	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. 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.

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II/0048	Update of Summary of Product Characteristics and Package Leaflet 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.	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 remaining three reports described the onset as 21 days, 19 months and "several weeks". Six

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					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. Although Rosiglitazone causes skin and anaphylactic reactions, the majority of the skin reactions were non-serious, in contrast to the anaphylactic reactions. Therefore, the presented data do not change the overall risk/benefit assessment. The CHMP concluded that the SPC and PL should be updated to reflect the mentioned data.
IB/0051	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	22/11/2006	n/a		
II/0046	Update of Summary of Product Characteristics Update of the section 4.6 of the Summary of Product Characteristics, following the publication of literature	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 in line with published literature that concluded that rosiglitazone crosses the placenta in the first trimester of human pregnancy. In that

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	which concluded that rosiglitazone crosses the placenta in the first trimester of human pregnancy.				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).
II/0047	Update of Summary of Product Characteristics and Package Leaflet 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.	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.
IB/0049	07_c_Replacement/add. of	07/09/2006	n/a		

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	manufacturing site: All other manufacturing operations ex. batch release				
IB/0050	33_Minor change in the manufacture of the finished product, 31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits	07/09/2006	n/a		
II/0044	Update of Summary of Product Characteristics and Package Leaflet 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 reported with rosiglitazone. The package leaflet has been updated accordingly. Annex II has been updated to reflect the Risk Management Plan.	01/06/2006	12/07/2006	SPC, Annex II, 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

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					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.
II/0043	Update of Summary of Product Characteristics, Labelling and Package Leaflet Update of section 4.8 (Undesirable Effects) of the Summary of Product Characteristics (SPC) and relevant sections of the Package Leaflet (PL).	27/04/2006	31/05/2006	SPC, Annex II, Labelling, PL	Following a review of the rosiglitazone safety information reported in 22 clinical studies and from post-marketing data, the MAH applied to revise section 4.8 (Undesirable Effects) of the SPC and relevant sections of the PL.
IA/0045	07_a_Replacement/add. of manufacturing site: Secondary packaging site	18/04/2006	n/a		
IB/0042	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	18/11/2005	18/11/2005	SPC, Labelling, PL	
IB/0041	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	18/11/2005	18/11/2005	SPC, Labelling, PL	

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N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/10/2005	n/a	PL	
IA/0039	47_b_Deletion of a strength	11/10/2005	n/a	SPC, Labelling, PL	
II/0032	Update of Summary of Product Characteristics Update of 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 metformin up to 2,000 mg daily) of 24 weeks duration performed in 197 children (10-17 years of age) with type 2 diabetes.	23/06/2005	27/07/2005	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. 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

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					recommended. Sections 4.2, 5.1 and 5.2 of the SPC have been updated to reflect this information.
R/0033	Renewal of the marketing authorisation	21/04/2005	08/07/2005	SPC, Annex II, Labelling, PL	
II/0031	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.8 of the Summary of Product Characteristics (SPC) to include information on the incidence of worsening or possible worsening of heart failure in a placebo-controlled one-year trial in patients with congestive heart failure NYHA class I-II. Additionally, the Marketing Authorisation Holder (MAH) took the opportunity to include a statement that not all pack sizes may be	21/04/2005	10/06/2005	SPC, PL	As a commitment to CHMP at the time of the initial marketing authorisation, the MAH undertook to perform a placebo-controlled clinical trial in patients with congestive heart failure NYHA I-II (trial 211). In the one-year trial (trial 211), worsening or possible worsening of heart failure occurred in 6.4% of patients treated with rosiglitazone, compared with 3.5% on placebo. In view of these findings, the currently approved contraindications and warnings and precautions remained unchanged, and section 4.8 of the SPC has been updated to reflect the results from trial 211.

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	marketed in section 6.5 of the SPC and section 1 of the Package Leaflet (PL) in accordance with the current QRD templates. Also a combined labelling text, combining the different pack-sizes of the same strength, was introduced.				
IB/0035	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	13/05/2005	n/a		
IB/0038	33_Minor change in the manufacture of the finished product	27/04/2005	n/a		
IA/0037	32_b_Change in batch size of the finished product - downscaling down to 10-fold	13/04/2005	n/a		
IA/0036	08_a_Change in BR/QC testing - repl./add. of batch control/testing site	13/04/2005	n/a		
IA/0034	39_Change/addition of imprints, bossing or other markings	13/04/2005	n/a	SPC, PL	

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II/0023	Extension of Indication Extension of indication and posology change: To increase the maximum approved rosiglitazone (RSG) dose to 8mg/day in combination with sulphonylurea (SU), and to add a triple oral combination indication for rosiglitazone with metformin (MET) and sulphonylurea, based on new clinical data.	18/11/2004	10/01/2005	SPC, PL	The change to increase the maximum approved RSG dose to 8 mg/day in combination with SU was supported by efficacy and safety data from 12 clinical studies. An incremental benefit in glycaemic control was seen in a meta-analysis comparing 4mg RSG and 8mg RSG in combination with an SU. This is in line with the dose-ordered effect of RSG, which has been described in monotherapy and in add-on therapy to MET. It was also noted that the potential for hypoglycaemia in combination with SU, either dual or triple therapy, warranted mention in section 4.4. In addition section 5.1 of the SPC has been updated to reflect 18-month interim data from an ongoing CHMP commitment study to assess the long-term effects of RSG on cardiovascular outcomes (RECORD). For detailed discussion of the additional indication, triple oral therapy, please refer to the scientific discussion: Avandia-H-268-II-23
II/0025	Update of Summary of Product Characteristics and Package Leaflet Update of Summary of Product	18/11/2004	10/01/2005	SPC, PL	The lipid lowering agent gemfibrozil has previously been shown to reduce the clearance of substrates metabolised by CYP2C9, 2C19, 1A2, 2C8, and UGT 1A1 and/or 1A3 (Preuksaritanont, 2002). In August

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	Characteristics and Package Leaflet Update of sections 4.4 and 4.5 of the 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.				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). On request from the CHMP the MAH applied for this type II variation to update sections 4.4 and 4.5 of the SPC to reflect the interaction data of the publication and the MAH's interaction 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 was requested 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

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2]/ amended on	Product Information affected[3]	Summary
					information.
II/0026	Update of Summary of Product Characteristics and Package Leaflet Update of Summary of Product Characteristics and Package Leaflet 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 Product Characteristics based on clinical trial and post-marketing data. The Package Leaflet has been updated accordingly.	18/11/2004	10/01/2005	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 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 yearly reports on hepato-biliary adverse reactions, especially hepatitis and acute liver failure, and including the adjudication on events of liver failure. The Package Leaflet has been updated accordingly.
IA/0030	36_ b_Change in shape or dimensions of the container/closure - other pharm. forms	07/12/2004	n/a		
IA/0029	07_a_Replacement/add. of manufacturing site: Secondary	27/11/2004	n/a		

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2]/ amended on	Product Information affected[3]	Summary
	packaging site				
IA/0028	07_a_Replacement/add. of manufacturing site: Secondary packaging site	22/11/2004	n/a		
II/0027	Quality changes Quality changes The Marketing Authorisation Holder applied to revise the specifications for the film coating of Avandia film coated tablets.	21/10/2004	22/10/2004		
II/0021	Update of Summary of Product Characteristics and Package Leaflet	03/06/2004	19/07/2004	SPC, Annex II, 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.
IB/0024	30_b_Change in supplier of packaging components - replacement/addition	13/07/2004	n/a		
N/0022	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/05/2004	n/a	PL	

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IB/0020	10_Minor change in the manufacturing process of the active substance	30/03/2004	n/a		