EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Avaglim

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
R/0033	Renewal of the Marketing Authorisation	14/04/2011	26/07/2011		On 3 December 2010 the European Commission issued a decision for the suspension of the marketing authorization of Avaglim, following a review of rosiglitazone-containing medicines because of reports of an increase in the risk of cardiovascular problems with rosiglitazone. The decision stated that the marketing authorisation should remain suspended until the marketing authorisation holder can provide convincing data to identify a patient population in which the clinical benefit of Avaglim clearly outweighs its risks. The Marketing Authorisation Holder has not submitted significant new data as part of the renewal application

[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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					and following the CHMP opinion to suspend all rosiglitazone-containing medicinal products. The CHMP concluded that the Benefit/Risk for Avaglim remains negative; consequently the five-year marketing authorization for Avaglim has not been renewed and expired on 29 June 2011.
IG/0034/G	This was an application for a group of variations. C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system, C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV, C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV, C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DDPS, C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of	06/01/2011	n/a	Annex II	IG/0034/G

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	the site undertaking pharmacovigilance activities				
A20/0029	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: Avaglim-H-675-A20-29-Assessment Report-Article 20
IA/0028	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	21/06/2010	n/a		
II/0025	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 investigating cardiac ischaemia. An updated Risk Management Plan (RMP) was submitted as part of this variation.	18/02/2010	09/04/2010	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: - 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

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	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 Cypriot local representative.				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 heart failure (fatal and non-fatal) (HR 2.10, CI 1.35-3.27) and bone fractures

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					(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/0026	Update of the Detailed Description of the Pharmacovigilance System (DDPS) including change of the Qualified Person for Pharmacovigilance (QPPV). Annex II	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

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	has been updated with the new version number. Update of DDPS (Pharmacovigilance)				version number of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements.
IA/0027	01_Change in the name and/or address of the marketing authorisation holder	15/12/2009	n/a	SPC, Labelling, PL	
II/0024	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	14/09/2009	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/0023	Update of the Product Information to include data from a completed clinical study (ADOPT). Section 5.1 of the Summary of Product Characteristics (SPC) has been updated to reflect the study findings. Section 4.8 of the SPC has 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 Package Leaflet including an update of the details of the local representatives.	23/07/2009	14/09/2009	SPC, 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

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	Update of Summary of Product Characteristics and Package Leaflet				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 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.
IA/0022	13_a_Change in test proc for active substance - minor change	30/09/2008	n/a		
IB/0021	33_Minor change in the manufacture	17/09/2008	n/a		

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	of the finished product				
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/09/2008	n/a	PL	
IB/0018	14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	02/07/2008	n/a		
IB/0019	14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	02/07/2008	n/a		
II/0017	Update of Summary of Product Characteristics and Package Leaflet 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. 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. This variation also refers to delete the contraindication for the use of rosiglitazone in combination with insulin in section 4.3 of the SPC. Additionally section 4.4 of the SPC has been updated with warnings regarding the risks of the use of	24/01/2008	03/03/2008	SPC, PL	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. In this variation also the contra-indication for the use of rosiglitazone in combination with insulin in section

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	rosiglitazone in combination with insulin. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				4.3 of the SPC has been deleted and section 4.4 of the SPC have been updated accordingly including a warning that the combination of rosiglitazone and insulin should only be used in exceptional cases and under close supervision. The Package Leaflet has been updated accordingly.
II/0013	Following a request from the CHMP, section 4.4 of Summary of Product Characteristics was updated in order to include a warning on the increased risk of haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The Package Leaflet was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/10/2007	23/11/2007	SPC, PL	The Pharmacovigilance Working Party (PhVWP) performed a review of drugs that might induce an increased risk of haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Glibenclamide, a sulfonylurea agent, is known to be directly responsible for haemolytic anaemia in patients with G6PD deficiency. After the review of other sulphonylureas, the PhVWP was of the opinion that haemolytic anaemia in patients with G6PD deficiency is a class effect of sulfonylurea agents. The PhVWP and the CHMP considered that given a potential class effect, a warning statement should be added in the product information of all sulphonylurea agents. Therefore, the Marketing Authorisation Holder (MAH) for Avaglim was requested to submit this type II variation in order to include a warning regarding the increased risk of haemolytic anaemia in patients with G6PD deficiency taking glimepiride.
IA/0016	11_a_Change in batch size of active substance or intermediate - up to 10-fold	08/11/2007	n/a		
IA/0015	09_Deletion of manufacturing site	08/10/2007	n/a		

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IA/0014	15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	13/09/2007	n/a		
II/0012	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. Update of Summary of Product Characteristics and Package Leaflet	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.
IA/0011	06_a_Change in ATC code: Medicinal products for human use	05/03/2007	n/a	SPC	
IA/0010	41_a_01_Change in pack size - change in no. of units within range of appr. pack size	14/02/2007	14/02/2007	SPC, Labelling, PL	
IA/0009	41_a_01_Change in pack size - change in no. of units within range of appr. pack size	14/02/2007	14/02/2007	SPC, Labelling, PL	
II/0008	Update of sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SPC and relevant sections of the PL.	14/12/2006	18/01/2007	SPC, Annex II, PL	Following a review of the safety information from integrated data of 25 clinical trials and from post-marketing data, the MAH updated section 4.8 of the SPC and relevant sections of the PL. A warning was also included in section 4.4 of the SPC regarding post-marketing reports of new-onset or

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	Update of Summary of Product Characteristics and Package Leaflet				worsening diabetic macular oedema with decreased visual acuity with thiazolidinediones, including rosiglitazone to make prescribers aware of the possibility of macular oedema if patients report disturbances in visual acuity.
II/0005	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	24/11/2006	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 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

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					during RSC use. The CHMP concluded that the SPC and PL should be updated to reflect the mentioned data.
II/0001	Update of the section 4.6 of the Summary of Product Characteristics (SPC), following the publication of literature which concluded that rosiglitazone crosses the placenta in the first trimester of human pregnancy. Relevant section of the Package Leaflet (PL) has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	27/10/2006	SPC, PL	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 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). The section 2 of the PL has been updated accordingly.
II/0002	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	27/10/2006	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 an 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 cannot be ruled out. As a consequence the MAH wished to update the SPC with information regarding these

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					risks. Sections 4.2, 4.4, 4.8 of the SPC and 2, 4 of the PL have been updated.
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/10/2006	n/a	Labelling	
IA/0007	25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	08/09/2006	n/a		
IB/0003	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	22/08/2006	n/a		
IA/0004	32_b_Change in batch size of the finished product - downscaling down to 10-fold	21/07/2006	n/a		

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