EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Riprazo

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
IG/0248	This was an application for a group of variations. C.I.z - C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
WS/0308/G	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. WS-0308-G was submitted for a group of variations consisting of one Type II variation and one Type IB variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Type II variation: Update of sections 4.4 and 4.8 of the SmPC to include information on 'anaphylactic reactions' reported post-marketing. The package	18/10/2012	22/11/2012	SPC, PL	WS-0308-G was submitted for a group of variations consisting of one Type II variation and one Type IB variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The safety update of the SmPC and Package Leaflet was based on the MAH's systematic review of all available information on anaphylactic reactions associated with the use of aliskiren from clinical studies and the MAH's post-marketing safety database. A number of cases of 'anaphylactic reaction' could be retrieved from the post-marketing database, of which six had no alternative explanation other than treatment with aliskiren. The product information of aliskiren-containing products (SPC sections 4.4 and 4.8) was therefore updated with

[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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	Leaflet has been updated accordingly. In addition, upon request by the CHMP, the MAH took the opportunity to update the SmPC wording related to the hydrochlorothiazide component of the fixed-dose combination. As a consequence, minor changes have been implemented in sections 4.2, 4.3 and 4.4 of the SmPC and the Package Leaflet has been updated accordingly. Type IB variation: Update of sections 4.4 and 4.8 of the SmPC, upon request by the CHMP following the assessment of FU2 026 for aliskiren and FU2 027 for aliskiren/HCTZ, to include further information about the ADR 'angioedema'. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.3.a- Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				relevant information. In addition, sections 4.4 and 4.8 of the SmPC was updated by the MAH to include further information about the ADR 'angioedema' after a request by the CHMP following the assessment of FU2 026 for aliskiren and FU2 027 for aliskiren/HCTZ. Following the assessment of the data provided, additional amendments not related to the scope of the present procedure were implemented to correct some inconsistencies in the changes to the Product Information approved in the previous WS173 procedure for Rasilez HCT.
IG/0232	This was an application for a group of variations. B.II.b.1.a - B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	14/11/2012	n/a		
IA/0080/G	This was an application for a group of	23/10/2012	n/a		

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	variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				
IG/0220/G	This was an application for a group of variations. B.I.a.1.f - B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.1.b - B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	09/10/2012	n/a		
R/0068	Renewal of the Marketing Authorisation	24/05/2012	23/08/2012	SPC, Annex II, Labelling, PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Riprazo remains positive, but considers that its safety profile is to be closely monitored for the following reasons: -the need of a close monitoring of fatal and non-fatal

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					cardiovascular events occurred with aliskiren use in combination with other RAAS blockers and CCBs, as well as of serious cardiovascular events occurred with aliskiren monotherapy -the need of a close for cerebrovascular adverse events of aliskiren both as monotherapy as well as in combination with other anti-hypertensive drugs, including other RAAS blockers taking into consideration both spontaneously reported data and clinical trial data Based upon the safety profile of Riprazo, the CHMP decided that the MAH should continue to submit yearly PSURs. Therefore, based upon the safety profile of Riprazo, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
IG/0209/G	This was an application for a group of variations. 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.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	17/08/2012	n/a		
IG/0206	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)	23/07/2012	n/a		

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IG/0196/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites, B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	13/07/2012	n/a		
WS/0189	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/04/2012	25/05/2012	SPC	Aliskiren is mainly eliminated through the hepatobiliary route. Renal excretion only accounts for 0.6% of the administered dose. No adjustment of the initial dosage is required in patients with mild to severe renal impairment, however caution should be exercised in patients with severe renal impairment. The MAH has conducted a study (Study SPP100A2262) to characterize the pharmacokinetics and safety of aliskiren in End-Stage Renal Disease (ESRD) patients receiving haemodialysis (HD). It is concluded that no dose adjustment is needed in patients with ESRD. A novel and important finding of the study is that aliskiren cannot be efficiently removed by HD. Based on the data of Study SPP100A2262, the MAH proposes to change the section 4.9 and 5.2 of the SmPC.
A20/0069	Article 20 Review On 20 December 2010, the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004 for all aliskiren containing medicinal products authorised in the centralised procedure and requested	16/02/2012	20/04/2012	SPC, Annex II, PL	Please refer to the Assessment Report: Riprazo-H-853-A20-69-Assessment Report-Article 20.

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	the CHMP to assess all the available data and its impact on the risk benefit balance for aliskiren-containing medicinal products and to give its opinion on whether the marketing authorisations for these products should be maintained, varied, suspended or revoked. The scope of the review was to assess the risk benefit balance of all aliskiren-containing medicinal products in the approved indication of hypertension in light of the emerging safety data from the ALTITUDE study in patients with diabetes at high risk for cardiovascular and renal events which lead to the premature study termination. Article 20 Review				
IG/0148/G	This was an application for a group of variations. 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 DD. 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	22/02/2012	n/a		

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WS/0191/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The specification of the active substance aliskiren has been tightened. The test procedures used for aliskiren have been updated. In addition, typographic errors have been corrected in the dossier. All those changes apply to both routes of synthesis of aliskiren (Synthesis B and synthesis C), where applicable. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits, B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure, B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised, B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or	16/02/2012	16/02/2012		

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	a starting material/intermediate				
WS/0145	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update to section 4.8 of the SmPC to include severe cutaneous adverse reactions including toxic epidermic necrolysis and oral mucosal reactions, following the assessment of PSUR 5. The MAH has submitted consequential changes to the Package Leaflet. In addition, minor changes have been made in the Section 2 of the Package Leaflet with regards to angioedema for Rasilez, Rasilez HCT, Riprazo and Sprimeo. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	20/10/2011	22/11/2011	SPC, PL	Toxic epidermal necrolysis (TEN) is considered severe cutaneous adverse reaction (SCAR) as it is severe, unpredictable, and drug-induced. TEN is characterized by extensive detachment of the epidermis and erosions of the mucous membranes. In response to request from CHMP, the MAH has conducted comprehensive review in which cases of SCARs have been identified where the causal relationship with aliskiren cannot be ruled out in the absence of alternative explanations. Considering the severity of the described reactions, the CHMP requested “SCARs” including “TEN” and “oral mucosal reactions” to be added in section 4.8 of aliskiren containing product SmPC.
WS/0146	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	20/10/2011	22/11/2011	SPC, PL	Arthralgia is a nonspecific symptom which can be associated with various medical conditions. The most frequent are osteoarthritis, gout, bursitis, infectious diseases, injury, osteomyelitis, and autoimmune diseases. However, it is also considered that hypersensitivity/allergic reactions sometimes manifest with systemic involvement including arthralgia. Joint swelling is also very commonly associated with the

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	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				above mentioned joint disorders, or could be linked to peripheral oedema or to systemic manifestation of hypersensitivity reactions. This review focused on arthralgia and joint swelling cases where underlying hypersensitivity reactions likely played a role in the development of arthralgia and where both conditions could have been due to the direct effect of aliskiren. In response to the request from CHMP, MAH conducted a comprehensive review of all cases of "Arthrlagia". Based on this new analysis, CHMP requested the addition of the ADR "Arthralgia" in section 4.8 of aliskiren containing product SmPCs.
WS/0169	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.3 of the Summary Product Characteristics (SmPC) to remove verapamil from the contraindications, and sections 4.4 and 4.5 of the SmPC, following the CHMP assessment of the data regarding the potential for interaction of aliskiren with verapamil, and the impact of p-gp inhibition on the distribution of aliskiren. The Package Leaflet has been updated accordingly. In addition, MAH took opportunity to update the contact details of local representatives in the PIL for Riprazo, Sprimeo and Riprazo HCT. This application is submitted in	22/09/2011	27/10/2011	SPC, PL	Contraindication with regards to concomitant use of aliskiren and the highly potent P-gp inhibitor ciclosporin and other potent P-gp inhibitors (verapamil, quinidine) was introduced on the basis of results from drug-drug interaction study. Subsequently, as a part of Rasilez FUM 015 MAH was requested to provide additional preclinical data evaluating the potential mechanism of the ciclosporin and other potent P-gp inhibitor interaction with aliskiren. A type II variation was approved to remove the contraindication against concomitant use of verapamil and aliskiren from the Summary of Product Characteristics of Rasilez and RasilezHCT (II/41 and II/05-G, approved in March 2011) and to include a statement with regard to potential for interaction with organic anionic transporting polypeptide (OATP) inhibitors and with rifampicin. Corresponding amendments were also introduced into the Patient leaflet. The present variation application is submitted to introduce the same changes to the Product Information

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	fulfilment of the FUM001 for Riprazo HCT and Sprimeo HCT. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				for all aliskiren-containing medicinal products. The proposed changes to the product information are acceptable. See scientific discussion EMA/H/C/xxx/WS/0169.
IG/0088/G	This was an application for a group of variations. 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 DD, 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	11/07/2011	n/a		
WS/0139/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To add a new manufacturing site Novartis Grimsby Ltd, UK, for the intermediates of aliskiren, respectively C3 and C6. Together with this change, several changes have been introduced to the	23/06/2011	23/06/2011		

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	reagents, solvents, starting material specifications and batch size at the proposed site. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer, B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size, B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits, B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method, B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter), B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation, B.I.b.2.a - Change in test procedure for AS or starting				

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	material/reagent/intermediate - Minor changes to an approved test procedure				
WS/0055	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.2 and 5.1 of the SmPC to include information about the efficacy and safety of aliskiren in elderly and very elderly hypertensive patients based on data from the AGELESS study. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	23/05/2011	SPC	AGELESS study was conducted in order to specifically evaluate the safety and efficacy of aliskiren and aliskiren/HCT in elderly (>65ys) and very elderly (>75 ys) hypertensive patients. Overall the results of this clinical study support the conclusion of a positive benefit/risk ratio in the use of the aliskiren+HCTZ as antihypertensive treatment of elderly and very elderly patients. However, the review of available data also suggests different response to the treatment of elderly and very elderly. As a result sections 4.2 and 5.1 have been updated by including information about the efficacy and safety of aliskiren in elderly and very elderly hypertensive patients.
WS/0098	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC to add the Adverse Drug Reaction 'hypersensitivity reactions' under post-marketing experience as requested by CHMP following PSUR review. The Package Leaflet has been updated accordingly. In addition, the MAH takes the opportunity to update the contact details in the Package Leaflet of the local representative in Poland. This application was submitted for a group of variations consisting of Type	14/04/2011	23/05/2011	SPC, PL	Following the review of PSUR 5 for aliskiren MAH was requested to consider updating the SmPC to add severe cutaneous adverse reactions (SCARs) and arthralgia. Conducted review of all cases of SCARs and of arthralgia did not demonstrate an evidence of a clear causal relationship between these events and aliskiren treatment. However, the analysis revealed a possible relationship between these events and hypersensitivity. Subsequently MAH has performed a detailed analysis of available data. The evidence presented is considered to support the inclusion of post-marketing events of "hypersensitivity" into the SmPC section 4.8 (undesirable effects) for aliskiren.

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	II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
WS/0073	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This type II variation concerns an update of sections 4.2 and 4.5 of the SPC in view of the results of study CSPP100A2112 investigating the potential interaction between aliskiren and grapefruit juice in healthy subjects. The Package Leaflet has been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/02/2011	18/03/2011	SPC	This type II variation concerns an update of section 4.5 of the SPC in view of the results of study CSPP100A2112 investigating the potential interaction between aliskiren and grapefruit juice in healthy subjects. Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and Cmax of aliskiren. Co-administration with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with aliskiren. This application was submitted for a Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.
WS/0028	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Summary of Product	20/01/2011	21/02/2011	SPC, PL	This type IB variation concerns an update of section 4.8 of the SPC, upon request by CHMP following the assessment of PSURs 4 and 5 for aliskiren, to add the ADR 'blood creatinine increase' under post-marketing experience. The Package Leaflet has been updated

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	Characteristics and Package Leaflet. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				accordingly. In addition, the MAH took the opportunity to make some minor editorial changes to the safety information already included in section 4.8 of the SPC. This application was submitted as a Type IB variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.
WS/0069	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This type IB variation concerns an update of sections 4.3, 4.4 and 4.8 of the SPC, upon request by CHMP following a review by the PhVWP of the risk of angioedema with aliskiren, to add the new contraindication 'hereditary or idiopathic angioedema' and to add further information about the risk of angioedema with aliskiren administration. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	16/12/2010	01/02/2011	SPC	This type IB variation concerned an update of sections 4.3, 4.4 and 4.8 of the SPC, upon request by CHMP following a review by the PhVWP of the risk of angioedema with aliskiren, to add the new contraindication 'hereditary or idiopathic angioedema' and to add further information about the risk of angioedema with aliskiren administration. The application was submitted for a Type IB variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. See scientific discussion EMA/H/C/XXXX/WS/0069.

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IB/0042/G	This was an application for a group of variations. B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative	28/01/2011	28/01/2011	SPC, Labelling, PL	

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	composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,				

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	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms, B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms				
IB/0043/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS,	27/01/2011	n/a		

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	starting material, reagent or intermediate used in the manufacture of the AS, A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS, B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IG/0032/G	This was an application for a group of variations. Update of Summary of Product Characteristics, Labelling and Package Leaflet To implement Core Data Sheet changes in the relevant sections of the EU SmPC. The proposed changes in the SmPC are also reflected in the corresponding sections of the labelling and PL. As part of the outcome of assessment of FUM 007, 5.2 of SmPC is updated to include data from paediatric study DAP-PEDS- 07-02. The "Annex II B. Conditions for the marketing authorisation" has been updated to include the key messages of the additional risk minimisation activities described in the EU Risk Management Plan, already in place in Member States.	21/12/2010	n/a	Annex II	This was an application for a group of variations. Core Data Sheet changes in the relevant sections of the EU SmPC are implemented. The proposed changes in the SmPC are also reflected in the corresponding sections of the labelling and PL. As part of the outcome of assessment of FUM 007, 5.2 of SmPC is updated to include data from paediatric study DAP-PEDS- 07-02. The "Annex II B. Conditions for the marketing authorisation" has been updated to include the key messages of the Additional Risk Minimisation Activities described in the EU Risk Management Plan, already in place in Member States. Core Data Sheet changes: Changes are made to SmPc, labelling and PL, in order to be consistent with relevant changes made to the Novartis Cubicin Basic Prescribing Information. DAP-PEDS- 07-02: A study was conducted to evaluate the pharmacokinetics of daptomycin after a single 8 mg/kg or 10 mg/kg dose of Cubicin as either a 1 or 2 hour infusion in paediatric subjects aged 2 to 6 years, inclusive, with proven or suspected Gram-positive infections who were receiving standard antibiotic

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	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 DD, 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				therapy. The mean exposure (AUC0-8) was approximately 429 and 550 µg*hr/ml after the administration of 8 and 10 mg/kg single doses, respectively, similar to the exposure seen in adults at the 4 mg/kg dose at steady state (495 µg*hr/ml). The pharmacokinetics of daptomycin appears to be linear in the dose range studied. The half life, clearance and volume of distribution were similar at both dose levels. Risk minimisation Activities: The additional risk minimisation activities mentioned in the Risk Management Plan in the form of dosage card and laboratory susceptibility testing leaflet were in place for Cubicin because of concerns over medication errors, severe skeletal muscle toxicity and interference with coagulation tests results. It was recognised that these measures are very important for the safe and effective use of the product, hence, the CHMP recommended that this was made a condition of the Marketing Authorisation.
WS/0037	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics, Annex II and Package Leaflet C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/09/2010	03/11/2010	SPC, Annex II, PL	This type II variation concerned an update of section 4.3 of the SPC to add a contraindication for the concomitant use of aliskiren and itraconazole, and section 4.5 of the SPC to add information regarding this interaction following the publication of a study in healthy subjects. The Package Leaflet has been updated accordingly. A study in healthy volunteers showed that itraconazole (100 mg) increases AUC and Cmax of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and the potent P-gp inhibitor itraconazole is contraindicated. In addition, the MAH took the opportunity to update the annexes in line with the latest QRD template (version 7.3). This application was submitted for a Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. See scientific discussion EMA/H/C/xxx/WS/0037.

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WS/0056	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Increase of the batch size for the intermediate B3 B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	21/10/2010	21/10/2010		
WS/0027	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This type IB variation concerns an update of section 4.8 of the SPC, upon request by CHMP following the assessment of PSUR 3 and PSUR 4, to include information about the ADR 'peripheral oedema'. The Package Leaflet has been updated accordingly. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Art 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	23/09/2010	15/10/2010	SPC, PL	This variation concerns an update of section 4.8 of the SPC, upon request by CHMP following the assessment of PSUR 3 and PSUR 4, to include information about the ADR 'peripheral oedema'. The Package Leaflet has been updated accordingly. The application was submitted for a Type IB variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Peripheral oedema has been reported with aliskiren use in the post-marketing setting. The detailed analysis of spontaneous reports showed that many cases were confounded by patient medical history or suspect concomitant medication. Nevertheless, a number of cases showed a positive de-challenge such that a causal relationship to treatment could not be excluded. Therefore, based on this analysis, and in accordance with CHMP's requests following assessment of PSUR 3 and PSUR 4 for aliskiren, the MAH applied for a variation to update the 'Undesirable effects' section of the SPC to add the text: "Post marketing experience: peripheral oedema (frequency unknown)". The Package Leaflet has also been updated accordingly.

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N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/10/2010	n/a	PL	
WS/0030	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	23/09/2010	23/09/2010		
IG/0011	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	01/07/2010	n/a		
II/0039	Update of the Detailed Description of the Pharmacovigilance system (DDPS). Update of DDPS (Pharmacovigilance)	18/02/2010	23/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (core version 8.0 and product specific version 6.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.
IB/0036	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	29/04/2009	n/a		
IB/0038	33_Minor change in the manufacture of the finished product	29/04/2009	n/a		
II/0034	Update of SPC section 5.1 to delete the existing sentence relating to elevated	19/03/2009	22/04/2009	SPC	The following sentence has been deleted from SPC section 5.1 based on the fact that currently no data are

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	plasma renin activity and cardiovascular outcomes. Update of Summary of Product Characteristics				available to directly link the reduction in renin activity induced by aliskiren with effects on cardiovascular outcomes: "Elevated PRA has been independently associated with increased cardiovascular risk in hypertensive and normotensive patients." as currently there is no evidence available proving that changes in renin activity induced by antihypertensive drugs might have an important role in cardiovascular disease.
II/0031	Update of SPC sections 4.3 and 4.4 to include a contraindication on the use in patients with prior history of angioedema and a warning of angioedema-type reactions as for other agents acting on the renin-angiotensin system respectively, following the CHMP assessment of PSURs. Furthermore, SPC section 4.8 has been revised regarding angioedema cases and the Package Leaflet has been updated in accordance with the SPC changes. Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	03/04/2009	SPC, PL	For aliskiren, cases of angioedema with relevant occurrence were reported in the postmarketing use. Following the assessment of the available data, the CHMP concluded that a contraindication for patients with a history of angioedema with aliskiren is needed. In addition, a warning of angioedema-type reactions as for other agents acting on the renin-angiotensin system has been added to SPC section 4.4 recommending that patients without a previous history who suffer angioedema with aliskiren should discontinue treatment and contact their doctor. Furthermore,the term "angioedema" has been added as a rare adverse drug reaction to SPC section 4.8.
II/0032	Update of SPC section 4.5 to include a statement regarding the potential interaction with non-steroidal anti-inflammatory agents (NSAIDs). The package leaflet has been amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	03/04/2009	SPC, PL	The MAH was requested to add a statement regarding the potential for interaction between NSAID's and agents acting on the Renin Angiotensin System to SPC section 4.5. As with other agents acting on the renin - angiotensin system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination of aliskiren

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					with an NSAID requires caution, especially in elderly patients. The package leaflet has been amended accordingly.
II/0033	Update of SPC section 4.4 to include a warning of events of renal dysfunction in at-risk patients and to amend the existing text for renal artery stenosis following the CHMP assessment of PSURs. SPC section 4.8 has been updated relating to events of renal dysfunction and acute renal failure during post-marketing experience. The package leafet has been amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	03/04/2009	SPC, PL	For aliskiren, cases of renal dysfunction with relevant occurrence were reported in the postmarketing use (PSUR 1 and PSUR 2). Following evaluation of the available postmarketing data, the CHMP concluded to add a warning to SPC section 4.4 that caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolemia (eg. due to blood loss, severe or prolonged diarrhea, prolonged vomiting, etc.), heart disease, liver disease or kidney disease. Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience.. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued. Furthermore, SPC section 4.8 was also amended.
IA/0037	32_a_Change in batch size of the finished product - up to 10-fold	11/02/2009	n/a		
IA/0035	07_a_Replacement/add. of manufacturing site: Secondary packaging site, 07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	11/02/2009	n/a		
II/0029	Update of or change(s) to the pharmaceutical documentation	23/10/2008	04/11/2008		
II/0026	Update of SPC section 4.3 "Contraindications" and section 4.5 "Interactions" following new information from a cyclosporine drug-drug interaction study (SPP100A2106),	24/07/2008	28/08/2008	SPC, Labelling, PL	The results of the cyclosporine interaction study in 14 subjects showed that concomitant cyclosporine administration increased AUC 4.5 to 5.5 fold with a lower dose of aliskiren (75 mg) than the authorised strengths (150 and 300mg). Also cyclosporine markedly increased

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	which was subject to a Follow-Up Measure. Further revisions were introduced to section SPC sections 4.4 "Warnings and Precautions for use" and 4.5. The package leaflet has been amended accordingly. In addition, minor corrections have been included in the relevant sections of SPC, labelling and package leaflet with regard to the active substance (aliskiren hemifumarate) and also for PL section 5. Update of Summary of Product Characteristics, Labelling and Package Leaflet				aliskiren t1/2. Hence, there is concern that the increase in AUC would be substantially higher with the approved aliskiren dosage, even exceeding the highest dose tested in humans. An additional concern is that aliskiren might distribute to tissues from which the medicinal product is normally absent in presence of a P-gp inhibitor, or preset at low levels because of the activity of P-gp. Non clinical and clinical data converge to show that P-gp is a major determinant of aliskiren bioavailability. In addition, literature data show that P-gp mediates tissue uptake of a variety of P-gp substrates and that P-gp inhibitors can markedly increase the tissue-to-plasma concentration ratios. Given the very limited safety data at increased exposure, and the risk for very large increase in tissue exposure, the CHMP concluded that the co-administration of cyclosporine and aliskiren poses serious safety concerns. Therefore, a contraindication for the concomitant administration with cyclosporine, a highly potent P-gp inhibitor, as well as with other potent P g inhibitors (verapamil, quinidine) is considered essential. Moreover, due to the risk for higher increase in tissue exposure than in plasma, caution should be advised during co administration with moderate P-gp inhibitors (ketoconazol, itraconazol, clarithromycin, telithromycin, erythromycin, amiodarone).
II/0030	Update of or change(s) to the pharmaceutical documentation	24/07/2008	29/07/2008		
II/0027	Update of the SPC section 4.4 and 5.1 following new information from a study (SPP100A2313) in patients with heart failure. Update of Summary of Product	30/05/2008	09/07/2008	SPC	Study SPP100A2313, a 12-week double-blind, randomised, placebo-controlled, 2-arm study of aliskiren 150 mg od added to standard therapy in patients with stable heart failure evaluated the overall safety and tolerability of aliskiren 150 mg when given in addition to standard therapy in hypertensive patients with stable

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	Characteristics				heart failure. The study included 302 patients with mild to moderate heart failure. Addition of 150 mg aliskiren showed a reduction of BNP levels by 25 %, although the clinical significance of this reduction is unknown. No statistically significant differences in signs and symptoms of heart failure were found and overall grading of patients according to NYHA classification remained unchanged.
II/0028	Update of SPC section 5.1 "Pharmacodynamic Properties" with efficacy data from a clinical study (study SPP100C2201) in patients with nephropathy. Update of Summary of Product Characteristics	30/05/2008	09/07/2008	SPC	Study SPP100C2201, a 6 monthly randomised, double-blind, placebo-controlled study investigated the effects of aliskiren (150mg / 300mg) on proteinuria in 599 patients with hypertension and Type II 2 diabetes mellitus in whom blood pressure had been previously controlled by means of an angiotensin receptor blocker (losartan) in combination with the optional use of other antihypertensive drugs (hydrochlorothiazide and/or amlodipine). The addition of 300mg aliskiren achieved an average reduction in the urinary albumin to creatinine (UACR) ratio of 12 mg/mmol (from 58 to 46 mg/mmol) compared to placebo. Aliskiren did not induce any significant effect on blood pressure or affect estimated GFR under these conditions. The clinical relevance of a reduction in UACR is not established in the absence of an effect on blood pressure. Furthermore, aliskiren was associated with an increased frequency (4.2% vs. 1.9% for placebo) in serum potassium concentration (? 6 mmol/l).
IB/0012	10_Minor change in the manufacturing process of the active substance, 12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	31/01/2008	n/a		
IB/0002	12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	15/11/2007	n/a		

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IB/0001	12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	15/11/2007	n/a		
IA/0013	11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		
IA/0018	11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		
IA/0017	11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		
IA/0014	11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		
IA/0016	11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		
IA/0019	11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		
IA/0015	11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		
IA/0020	11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		