Rasitrio

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IG/0349	B.III.1.a.4 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Deletion of certificates (in case multiple certificates exist per material)	27/08/2013	n/a		
WS/0407	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	27/06/2013	26/07/2013	SmPC and PL	A drug-drug interaction between aliskiren and furosemide (a loop diuretic) has been previously identified. Based on the fact that loop diuretics depend on their renal excretion and these drugs are actively secreted by renal transporters

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	Update of sections 4.4 and 4.5 of the SmPC of aliskiren and aliskiren fixed-dose combination products to include a warning statement concerning the concomitant use of aliskiren and torasemide in patients with heart failure (section 4.4) and to include information on the potential for drug-drug interaction between aliskiren and torasemide (section 4.5) as per CHMP request expressed in the conclusions of Rasilez HCT PSUR 4 and 5 assessment report. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				of the proximal tubule, it can be considered that from a mechanistic point of view a drug-drug interaction between aliskiren and torasemid (another loop diuretic) is plausible. No formal aliskiren/torasemid drug-drug interaction study has been performed. The available clinical data doesn't show that higher doses of torasemid were needed when taken together with aliskiren. The post-marketing data doesn't indicate a higher incidence of AEs attributable to a reduced torasemide effect when aliskiren is taken together with torasemide. These observations don't support the DDI hypothesis nevertheless such interaction cannot be out-ruled either. Therefore, the CHMP accepted the MAH's proposal to include a warning statement concerning the concomitant use of aliskiren and torasemide in patients with heart failure (SmPC section 4.4) and to present the available information on the potential for drug-drug interaction between aliskiren and torasemide (SmPC section 4.5).
IA/0033	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	05/06/2013	n/a		
WS/0374	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The WSA updated section 4.4. of the SmPCs of all aliskiren containing products with regard to the combined use of agents acting on the renin angiotensin aldosterone system (dual blockade of the renin-angiotensin-aldosterone system (RAAS)) and the associated risk of symptomatic hypotension.	30/05/2013	04/07/2013	SmPC and Labelling	Based on a review of the published literature and available clinical trial and post marketing data the CHMP agreed with the MAH's conclusion that there is a higher risk of hypotension in patients taking aliskiren in combination with other agents acting on the renin-angiotensin-aldosterone system (RAAS) such as angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs). Therefore, the MAH's proposal to update section 4.4. of the SmPCs of all aliskiren containing products with regard to

	In addition, the MAH took the opportunity to update the list of local representatives in the 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				the combined use of agents acting on the renin angiotensin aldosterone system (dual blockade of the renin-angiotensin-aldosterone system (RAAS)) and the associated risk of symptomatic hypotension was found acceptable by the CHMP.
WS/0375	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 of all aliskiren containing products in order to: - include the adverse reactions “liver disorder”, “jaundice”, “hepatitis” and “liver failure” based on several reported cases of “liver disorder” accompanied by clinical symptoms and laboratory evidence of marked hepatic dysfunction, 7 cases of “jaundice” (5 of them with dechallenge+), 2 cases of “yellow skin” (both with dechallenge +) and 4 fatal cases of “hepatic failure” (including one case of “liver failure fulminant” with consequent liver transplant). - change the system organ class (SOC) for the ADR “dizziness” from Nervous system disorders to Cardiac disorders and the SOC for “edema peripheral” from “General disorders and administration site conditions” to “Cardiac disorders” in order to conform to the primary path for the mapping of terms in the most current MedDRA version. The Package Leaflet was updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	30/05/2013	04/07/2013	SmPC and PL	Based on the data resulted from a systematic review of available information on liver events from the published literature, the MAH’s safety database and clinical trial database, the MAH proposed the inclusion of ADR “liver disorder” in the SmPC section 4.8 of all aliskiren containing products. This proposal was found acceptable by the CHMP since it was supported by several reported cases of “liver disorder” accompanied by clinical symptoms and laboratory evidence of marked hepatic dysfunction. In addition, at the CHMP request, the MAH accepted to include “jaundice”, “hepatitis” and “liver failure” as ADRs in section 4.8 of the SmPC of all liskiren containing products under the system organ class (SOC) “Hepatobiliary disorders” with the frequency “unknown”. The CHMP based its request on 7 cases of “jaundice” (5 of them with dechallenge+), 2 cases of “yellow skin” (both with dechallenge +) and 4 fatal cases of “hepatic failure” (including one case of “liver failure fulminant” with consequent liver transplant). In addition, change of the SOC for the ADR “dizziness” from “Nervous system disorders” to “Cardiac disorders” and the SOC for ADR “edema peripheral” from “General disorders and administration site conditions” to “Cardiac disorders” was implemented in order to reflect the latest primary path for the mapping of terms presented in the most current MedDRA version.

	clinical, clinical or pharmacovigilance data				
WS/0287	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the RMP for aliskiren containing products addressing the obligations introduced as a result of Article 20 procedure and Rasilez R-62/Riprazo R-68 renewal procedure. Annex II has been updated to reflect that this commitment has been fulfilled. C.I.3.z - 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 - Other variation	21/03/2013	10/04/2013	Annex II	The MAH submitted a consolidate RMP version applicable for aliskiren, aliskiren monotherapy, and its three FDCs in order to address the obligations introduced as a result of Article 20 procedure and Rasilez R-62/Riprazo R-68 renewal procedures. The CHMP concluded that RMP version 9 adequately describes all the safety concerns, the planned pharmacovigilance activities and the interventions designed to identify, characterise, prevent or minimise the risks. Therefore the MAH's proposal to remove the above commitment from Annex II is acceptable.
WS/0316	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.4, 4.5, 4.7, 4.8 and 5.2 of the SmPC in order to implement in the SmPCs of the fixed dose combination products containing aliskiren the agreed changes for the SmPC of Rasilez following the conclusion of the renewal procedure. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/01/2013	18/02/2013	SmPC, Annex II, Labelling and PL	Update of sections 4.2, 4.4, 4.5, 4.8 and 5.2 of the SmPC in order to implement the agreed changes for the SmPC of Rasilez (aliskiren mono therapy product) across the SmPCs of the fixed dose combination products containing aliskiren. In addition the SmPC section 4.7 was updated in a consistent manner across the combination products indicating that no studies have been performed on the ability to drive. The PL section 2 includes the information that the 300 mg aliskiren taken alone doesn't reduce the blood pressure of the majority of patients older than 65 compared to the 150 mg dose.

WS/0327	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.8 and 5.2 of the SmPC in order to add pharmacokinetic and safety information related to paediatric population following the assessment of the study CSPP100A2256. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	17/01/2013	18/02/2013	SmPC	Based on the results of a clinical study conducted in paediatric population the MAH updated the SmPC in order to confirm that: based on the available data in children posology recommendations in children cannot be made (SmPC section 4.2), the safety and pharmacokinetics profiles in children are expected to be similar to the one in adults (SmPC section 4.8 and 5.2). The CHMP agreed with the proposed updates.
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
WS/0280	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The MAH proposed the update of sections 4.4 and 4.5 of the Summary of Product Characteristics (SmPC) in order to update the information regarding aliskiren interaction with furosemide following completion of the drug-to-drug interaction study CSPP100A2255. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC -	13/12/2012	21/01/2013	SmPC	The MAH performed the present study [CSPP100A2255] with the aim of assessing whether a pharmacodynamic (diuretic efficacy) interaction exists between aliskiren and furosemide in heart failure patients. The study assessed the effect of a single (150 mg) and multiple doses (150 and 300 mg/day) of aliskiren on pharmacokinetics, efficacy and safety of once daily 60 mg furosemide at steady state in patients with chronic heart failure. Overall, the study data suggest that aliskiren may decrease the efficacy of furosemide. Results of study CSPP100A2255 are the basis of a proposal for a modification of SmPC text to update the sections 4.4 and 4.5 of the SmPC.

	Change(s) with new additional data submitted by the MAH				
WS/0309	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This submission presents the active treatment phase of the ALTITUDE trial. The MAH required to update the Annex II by amending the relevant obligation deriving from Article 20 procedure. In addition the MAH proposed the update of section 5.1 of the SmPC with new data of the ALTITUDE STUDY. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	13/12/2012	21/01/2013	SmPC and Annex II	The MAH submitted final results and study report for the active treatment phase for ALTITUDE trial. The MAH was required to update the Annex II by amending the obligation deriving from Article 20 procedure as below. The MAH shall submit the final study report of the ALTITUDE study, including the 1-year safety extension phase covering the results of the active treatment phase relevant to the two different cut-off dates.
IB/0015	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	24/08/2012	22/11/2012	SmPC	
II/0016	This type II variation concerns the update of sections 4.9 and 5.2 of the SmPC in order to add the information on the pharmacokinetics of aliskiren in patients with end stage renal disease receiving haemodialysis following completion of the study SPP100A2262. C.I.3.b - Implementation of change(s) requested	18/10/2012	22/11/2012	SmPC	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)

	following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				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.
II/0017	This type II variation concerns the update of sections 4.9 and 5.2 of the SmPC in order to add the information on the pharmacokinetics of aliskiren in patients with end stage renal disease receiving haemodialysis following completion of the study SPP100A2262. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/10/2012	22/11/2012	SmPC and PL	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.
WS/0277	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the existing amlodipine information in section 4.5 of the SmPC in line with the revised drug interactions section for Norvasc (amlodipine monotherapy) approved as part of the recent article 30 procedure EMEA/H/A-30/1288 for amlodipine products. In addition, section 4.5 of the SmPC has been updated with information about the potential drug interaction between amlodipine and simvastatin.	18/10/2012	22/11/2012	SmPC	The following information was included in the SmPC as part of this procedure: Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects. Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the

	This variation followed 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				elderly. Clinical monitoring and dose adjustment may thus be required. There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, Hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers. Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine. In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia. In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.
IA/0026	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	14/11/2012	n/a		
WS/0278	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	18/10/2012	n/a	SmPC and PL	The changes to the product information of Rasilamlo and Rasitrio proposed by the MAH on the basis of the harmonised text for amlodipine monotherapy (Norvasc), that was adopted by the CHMP following the recent article

	Update of sections 4.2, 4.4, 4.6, 4.8 and 5.2 of the SmPC in order to harmonise the existing wording related to the amlodipine compound in line with the latest SmPC of Norvasc (amlodipine monotherapy) approved as part of the recent article 30 procedure EMEA/H/A-30/1288. The Package Leaflet has been updated in accordance. This variation followed 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				30 procedure, are acceptable to the CHMP. There is no change to the benefit-risk balance of the products, which remains positive.
WS/0308/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. 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 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	18/10/2012	n/a	SmPC and 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 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

	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				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.
WS/0310/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. All the variations relate to the active substance aliskiren or starting material/reagent/intermediate used in the process of aliskiren Addition of Novartis Grimsby Ltd, UK as additional manufacturer of intermediates C3 and C6 Change in batch size of intermediate C6 Change to specifications of raw materials, reagents and solvents used 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	18/10/2012	n/a		

	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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
WS/0279	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 5.3 the SmPC in order to add non-clinical information in alignment with the wording previously approved in the Article 30 of amlodipine	19/07/2012	10/09/2012	SmPC	In 2011 a review of the SmPCs of amlodipine-containing products was conducted in Europe leading to a harmonized European amlodipine label. As a consequence, MAH has proposed to update the SmPC of the aliskiren based fixed-dose combination products containing amlodipine based on the harmonized European amlodipine label. With this procedure MAH has updated non-clinical information in the

	products. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				section 5.3 of the SmPC concerning reproductive toxicology, impairment of fertility and information on carcinogenesis and mutagenesis.
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		
IA/0021	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	16/08/2012	n/a		
IA/0014/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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		
IA/0013	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur.	16/07/2012	n/a		

	Monograph - Updated certificate from an already approved manufacturer				
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		
IA/0012	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	09/07/2012	n/a		
IB/0008/G	This was an application for a group of 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	02/07/2012	n/a		

	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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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 a starting material/intermediate B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IG/0193/G	This was an application for a group of 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.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	19/06/2012	n/a		

	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				
II/0003/G	This was an application for a group of variations. Update of section 4.8 of the SmPC in order to include arthralgia, severe cutaneous adverse reactions including toxic epidermic necrolysis and oral mucosal reactions as adverse reactions following the assessment of PSUR 5. The Package Leaflet were proposed to be updated in accordance. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	19/04/2012	25/05/2012	SmPC and 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. 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 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.
A20/0001	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 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.	16/02/2012	20/04/2012		Please refer to the Assessment Report: Rasitrio-H-2017-A20-01-Assessment Report-Article 20.
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	22/02/2012	n/a		

	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				