EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Rasilamlo

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
PSUSA/00089	Periodic Safety Update EU Single assessment - ALISKIREN, AMLODIPINE (AS BESYLATE)	23/04/2015	19/06/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/00089.
IA/0103/G	This was an application for a group of variations B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new	15/04/2015	n/a		

[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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	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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IA/0102/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	16/03/2015	n/a		
WS/0581	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final study report for the non-interventional study CSPP100A2414 – A cohort study to assess various safety outcomes in aliskiren initiators using US claims data.	26/02/2015	n/a		

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
WS/0699/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. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation A.1 - Administrative change - Change in the name and/or address of the MAH	22/01/2015	19/06/2015	SmPC, Labelling and PL	
WS/0588	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	18/12/2014	n/a		
IG/0484/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	12/11/2014	n/a		

	site				
IB/0096	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	03/10/2014	n/a		
WS/0561	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final study report for the non-interventional study CSPP100A2415 – a cohort study including a nested case-control analysis using data from the United States IMS PharMetrics PlusTM health plan claims database – assessing the prevalence and incidence of angioedema among patients with hypertension treated with aliskiren or other antihypertensive medications in the US. The requested worksharing procedure proposed no amendments to the PI. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/09/2014	n/a		N/A
A31/0084	On 17 April 2013, further to the emergence of new evidence from the scientific literature on dual RAS blockade therapy and given the seriousness of the identified safety concerns, the Italian Medicines Agency (AIFA) initiated a review under Article 31 of Council Directive 2001/83/EC, requesting the Pharmacovigilance Risk Assessment Committee (PRAC) to issue a recommendation on the benefit-risk of dual RAS blockade therapy through the	22/05/2014	09/09/2014	SmPC and PL	For further information please refer to the Renin-angiotensin-system (RAS)-acting agents Article 31 referral - Assessment report.

	combined use of angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin II receptor blockers (ARBs) or aliskiren and to determine whether any regulatory measures should be taken on the marketing authorisations of the products involved in this procedure.				
IG/0443	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	20/08/2014	n/a		
PSUV/0090	Periodic Safety Update	25/04/2014	27/06/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0090.
WS/0500	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	20/02/2014	n/a		
IA/0092/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change	14/02/2014	n/a		

	in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				
WS/0481	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	23/01/2014	27/06/2014	SmPC and Annex II	Proteinuria has been identified as an independent risk factor for loss of kidney function or end-stage renal disease in diabetic patients. Earlier studies have indicated that proteinuria has been associated with increased renal as well as cardiovascular risk. A significant reduction in albuminuria has been achieved with the use of renin inhibition through aliskiren. Therefore it was hypothesized that aliskiren would offer additional renal and cardiovascular protection when administered on top of other RAS blockers, leading to the design of ALTITUDE. ALTITUDE was a double-blind placebo-controlled, randomized trial that enrolled patients with Type 2 diabetes and nephropathy as determined by macro-/microalbuminuria and/or eGFR <60 mL/min/1.73 m2. Nearly half of the patients also had significant cardiovascular disease. Patients with uncontrolled hypertension were excluded. Aliskiren was tested against placebo when added to standard therapy including an ACEI or ARB. The primary objective of the ALTITUDE study, was to determine whether aliskiren, compared to placebo, delays the occurrence of cardiovascular and renal complications when added to conventional treatment in patients with type 2 diabetes at high risk for cardiovascular and renal events. As part of this procedure the MAH submitted the final CSR of the study fulfilling in this way the obligation mentioned in Annex II of all aliskiren containing products. In addition the MAH updated the section 5.1 of the SmPC in order to

					reflect the final results of the ALTITUDE study including the 1 year safety extension phase. The efficacy results did not indicate any advantage of adding aliskiren on top of standard therapy including an ACEI or ARB. The CHMP considers that, the presented data consistently suggest that the combination of inhibitors/blockers of the renin-angiotensin system lowers proteinuria and in addition increases the risk of cardiovascular or renal events in high cardiovascular risk patients. The CHMP concludes that the complete data of the ALTITUDE study do not add any new information to the benefit/risk profile of aliskiren in the approved hypertension indication and the benefit/risk balance of the aliskiren containing products remains positive. Moreover, it confirms the appropriateness of the wording regarding the contraindication for dual RAS blockade in high-risk diabetic patients, changes that were implemented at the time the preliminary results of ALTITUDE trial were made available. The CHMP considers that the proposed updates of section 5.1 of the SmPC reflect in an appropriate manner the relevant findings reported in ALTITUDE CSR.
WS/0480	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/01/2014	n/a		The MAH submitted the final CSR for APOLLO study. APOLLO study was designed to determine whether treatment with an aliskiren-based regimen in part combined with amlodipine or hydrochlorothiazide compared to a non-aliskiren based regimen, both on top of non-study BP lowering agents, where applicable, reduces the risks of major CV events (composite of CV death, non-fatal MI, non-fatal stroke and significant heart failure), and to determine whether treatment with an aliskiren-based regimen compared to a non-aliskiren based regimen prevents decline in the ability to perform everyday

					activities independently, or/and prevents decline in renal function and reduces total mortality. In view of the preliminary findings in the ALTITUDE trial (aliskiren treatment of type 2 diabetic patients with renal dysfunction on top of standard RAS blocking therapy) which was terminated early in December 2011 based on futility and potential increases in adverse events in the aliskiren group, it was agreed with regulatory authorities to contraindicate the use of aliskiren in diabetic hypertensive patients on concomitant RAS blocker therapy. Many patients enrolled in APOLLO were diabetic and were receiving another agent acting on the renin-angiotensin system (RAS) such as an ACEI or and ARB as standard of care, and it was decided to exclude them from APOLLO. Following the exclusion of diabetics from the study, Novartis concluded that the study in its current design would not provide the needed information about the efficacy and safety of aliskiren in elderly hypertensive patients within the required timeframe and decided in agreement with Health Authorities to terminate the study early. At the time of the early termination of the APOLLO study, a total of 1759 patients had been randomized as against the originally planned 11,000 patients. A total of 25 primary CV composite endpoints had accrued in the study as against the planned 2000. These low numbers significantly limit interpretation of the results. The CHMP considers that the presented data set does not add new significant information either for safety or efficacy of aliskiren because of the study limitations (premature termination of the study). The safety findings are consistent with the known safety profile of aliskiren in the general hypertensive population. Despite the fact that the

					study enrolled a vulnerable elderly population with elevated cardiovascular risk and that the incidence of adverse events and serious adverse events was low the limited data set does not allow drawing any meaningful conclusion on the safety profile of aliskiren when used in elderly patients at the highest approved strength (300 mg). The CHMP considers that this new data does not warrant any SmPC changes. The premature termination of the APOLLO study leaves unsolved the problem of the dose-response of aliskiren in elderly hypertensive patients. This area of missing information is reflected in the RMP of the aliskiren containing products and appropriate pharmacovigilance activities are employed in order to collect the needed data. Study CSPP100A2370 (ASSESS) is currently planned as a follow up to APOLLO, designed to evaluate the efficacy and safety of alikiren containing products in elderly patients. The CHMP concludes that the worksharing variation is approvable and the risk/benefit balance of alsikiren containing products in the approved indication remains positive.
IG/0396	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	10/01/2014	n/a		
WS/0467	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	19/12/2013	n/a		

WS/0373	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	24/10/2013	03/12/2013	SmPC and PL	In a paper published in 2011 it was described that orange and apple juice reduced the plasma concentrations of aliskiren. This paper was reviewed by the MAH and since the results with orange or apple juice were pertinent to the use of aliskiren, an update to the Summary of Product Characteristics was proposed in order to add a statement for not recommending the concomitant use of aliskiren with orange or apple juice. When combined with all available data (clinical trial, literature and post-marketing), the results of the study described in the above mentioned paper showed that the bioavailability of aliskiren is most sensitive to co-administration with food in general. The available clinical data do not suggest an additive effect of different types of foods and/or drinks, however the potential for decreased aliskiren bioavailability due to this additive effect has not been studied and therefore cannot be excluded. Literature data indicate that vegetable components or extracts may decrease aliskiren bioavailability. Therefore, the CHMP considered that based on the available data the concomitant consumption of vegetable components or extracts (including herbal teas and fruit juices) should be avoided in conjunction with aliskiren intake.
IB/0082	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	17/10/2013	03/12/2013	SmPC	
WS/0412	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	19/09/2013	03/12/2013	SmPC	The MAH submitted the final results of ASTRONAUT study. The ALTITUDE study was designed to expand the initial indication of aliskiren (ALI) exploring whether, in patients

	Update the SmPC section 5.1 of all aliskiren containing products in order to reflect the relevant efficacy and safety information reported in ASTRONAUT (CSPP100A2368) Clinical Study Report. 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				with type 2 diabetes at high risk for cardiovascular and/or patients with renal events, ALI at a target dose of 300 mg o.d. (compared to placebo), on top of conventional treatment (either angiotensin converting enzyme inhibitor or angiotensin receptor blocker), reduces cardiovascular and renal morbidity and mortality. On 14 December 2011, the independent Data Monitoring Committee (DMC) of the ALTITUDE trial recommended the study to be halted due to futility and potential for excess harm in patients receiving ALI (non-fatal stroke, renal complications, hyperkalaemia and hypotension in this high-risk study population was observed). The submitted clinical study report confirms previously submitted and assessed ASTRONAUT preliminary results and did not show a significant benefit of adding aliskiren to a standard therapy including an ACEI or ARB in patients hospitalized with a recent episode of AHF, neither with respect to the primary endpoint (CV death or HF re-hospitalization within 6 months), nor with respect to key secondary endpoint (first confirmed occurrence of either CV death or HF rehospitalisation within 12 months). The subgroup analysis showed a statistically significant interaction of treatment by diabetes status at baseline for the composite of CV death and HF re-hospitalization within 12 months and all-cause mortality within 12 months, showing excess of CV events and the increase in all-cause death in the aliskiren group in diabetic patients. In the subgroup of patients with diabetes mellitus the hazard ratio was 1.64 in favour of placebo (95% Confidence Interval: 1.15-2.33), whereas the hazard ratio in the subgroup of patients without diabetes was 0.69 in favour of aliskiren (95% Confidence Interval: 0.50-0.94); p-value for interaction = 0.0003.

					An increased incidence of hyperkalaemia (20.9% versus 17.5%), renal impairment/renal failure (16.6% versus 12.1%) and hypotension (17.1% versus 12.6%) was observed in the aliskiren group compared with placebo. As it concerns the impact of the ASTRONAUT preliminary results on the safety profile of aliskiren and on the product information, the CHMP considers that the currently approved aliskiren product information is adequately updated in this regard in sections 4.3 and 4.4 (i.e. contraindication of dual RAAS blockade in diabetic and/or renal disease patients, and a warning for dual blockade use in all other patients). The CHMP concludes that the presented data doesn't raise any additional safety concerns besides those already reflected in the product information and that the overall the benefit/risk of aliskiren containing products remains unchanged. The agreed text included in section 5.1 of the SmPC is considered by the CHMP as appropriately reflecting the relevant findings from ASTRONAUT study.
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. 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	27/06/2013	05/08/2013	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 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

	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				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).
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	30/05/2013	27/06/2013	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

	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-clinical, clinical or pharmacovigilance data				"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.
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. 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	30/05/2013	27/06/2013	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 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.
IA/0080	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	06/05/2013	n/a		
WS/0287	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	21/03/2013	22/04/2013	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

	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				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/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	25/02/2013	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.
WS/0316	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	17/01/2013	25/02/2013	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

	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				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.
IB/0075	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	04/02/2013	n/a		
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
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	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.

	MAH				
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 - Change(s) with new additional data submitted by the MAH	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.
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	18/10/2012	30/11/2012	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

	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				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 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/0278	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, 4.6, 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	18/10/2012	30/11/2012	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 30 procedure, are acceptable to the CHMP. There is no change to the benefit-risk balance of the products, which remains positive.

	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				
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. 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	18/10/2012	30/11/2012	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 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.
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 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	18/10/2012	n/a		

	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 products. C.I.4 - Variations related to significant modifications	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 section 5.3 of the SmPC concerning reproductive toxicology, impairment of fertility and information on carcinogenesis and mutagenesis.

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
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/0071	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/0067	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	16/07/2012	n/a		
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		

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 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	19/06/2012	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. 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	19/04/2012	25/05/2012	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) 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.
A20/0016	Article 20 Review	16/02/2012	20/04/2012	SmPC, Annex	Please refer to the Assessment Report: Rasilamlo-H-2073-

	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.			II and PL	A20-16-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 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		

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.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.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.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	16/02/2012	16/02/2012		

IA/0015/G	This was an application for a group of variations. 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 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	16/12/2011	n/a		
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. 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 Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	20/10/2011	09/12/2011	SmPC and 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 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/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 Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	20/10/2011	09/12/2011	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.
II/0003	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/10/2011	09/12/2011		
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	22/09/2011	27/10/2011	SmPC and 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

	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 Pgp 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 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				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 for all aliskiren-containing medicinal products. The proposed changes to the product information are acceptable. EMA/H/C/xxx/WS/0169.
WS/0168	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, minor changes have been made in the Section 2 of the Package Leaflet with regards to angioedema. This application is submitted in fulfilment of the FUM 004 for Riprazo HCT and FUM 003 for 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	22/09/2011	27/10/2011	SmPC and PL	Following the review of PSUR 5 for aliskiren MAH conducted review of all cases of severe cutaneous adverse reactions (SCARs) and of arthralgia. The analysis revealed a possible relationship between these events and hypersensitivity. The evidence presented has resulted in an update to the Summary of Product Characteristics (SmPC) for Rasilez, Sprimeo, Riprazo and Rasilez HCT to add hypersensitivity as a post-marketing adverse event in the section 4.8 of the SmPC. Corresponding amendments were also introduced into the Package Leaflet. The present application is submitted to introduce the same changes to the Product Information of Rasilamlo, Riprazo HCT and Sprimeo HCT. In addition, minor changes have been made in the Section 2 of the Package Leaflet in regards to angioedema.

WS/0167	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 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 Rasilamlo/Riprazo HCT. This application was submitted for a Type II 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	22/09/2011	27/10/2011	SmPC	
WS/0165	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	22/09/2011	27/10/2011	SmPC	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)

	Update of sections 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. This application is submitted in fulfilment of the FUM 002 for Riprazo HCT, Sprimeo HCT and Rasilamlo. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				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 demonstrating no clinically meaningful additional blood pressure reduction by increasing the dose to 300 mg in the majority of elderly patients. Sections 4.2 has been updated with this information. Furthermore, section 5.1 has been updated by including information about the efficacy and safety of aliskiren in elderly and very elderly hypertensive patients.
IA/0002/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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) A.7 - Administrative change - Deletion of manufacturing sites	23/08/2011	n/a		
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 DLPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	11/07/2011	n/a		

	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				