Rasilez

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
IAIN/0131	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	23/02/2023		Annex II and PL	

[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).

IA/0130	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)	13/01/2023	n/a		
IB/0129	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/11/2022	n/a		
PSUSA/89/20 2109	Periodic Safety Update EU Single assessment - aliskiren, aliskiren / hydrochlorothiazide	10/06/2022	n/a		PRAC Recommendation - maintenance
IA/0128/G	This was an application for a group of variations. B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form A.7 - Administrative change - Deletion of manufacturing sites A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	28/01/2022	03/02/2023	SmPC, Annex II, Labelling and PL	
IA/0126	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or	15/04/2021	n/a		

	manufacturer of a novel excipient				
IB/0125/G	This was an application for a group of variations. 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.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change 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 B.II.c.2.d - Change in test procedure for an excipient	22/10/2020	n/a		

	- Other changes to a test procedure (including replacement or addition) B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation 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				
WS/1818	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	28/05/2020	n/a		
WS/1581	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	05/09/2019	n/a		

PSUSA/89/20 1809	Periodic Safety Update EU Single assessment - aliskiren, aliskiren / hydrochlorothiazide	11/04/2019	n/a		PRAC Recommendation - maintenance
WS/1371	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, 4.8 and 5.1 of the SmPC of Rasilez and Rasilez/HCTZ SmPC in order to reflect the results from paediatric study CSPP100A2365E2 (a multicenter, 52 to 104 week extension study to evaluate the long term growth and development of pediatric hypertensive patients 6–17 years of age treated previously with aliskiren) provided as per the requirement of article 46. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement minor amendments in sections 4.2, 4.3, 4.5 and 4.7, 5.2 of Rasilez SmPC and package leaflet in alignment with Rasilez/HCTZ product information, as well as an editorial change in Annex II. Moreover, section 4.2 of the Rasilez/HCTZ SmPC has been updated to cross refer to sections 4.8, 5.1, and 5.2 in alignment with Rasilez SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/10/2018	09/10/2019	SmPC, Annex II and PL	Study CSPP100A2365E2 extension of the core study (CSPP100A2365E), evaluated the long-term safety in terms of growth and development of children 6-17 years of age with hypertension (primary or secondary) at baseline in the core study, previously treated with aliskiren. Overall, 106 paediatric patients aged 6 to 17 years with hypertension (primary or secondary) at baseline in the core study, previously treated with aliskiren, were enrolled in this 52 to 104 week off-therapy non-interventional observational extension study. The long-term safety is evaluated in terms of growth and development, through height and weight measurement, with added neurocognitive and renal function evaluations as follow-up measures performed only in patients with secondary hypertension (19 patients). In the primary analysis, there were no statistically significant differences in the mean changes in weight, height, or BMI between the treatment groups (aliskiren compared to the enalapril) from baseline to long term visit (Week 104). In patients after 104 weeks (Week 156), there were LS mean decreases from Baseline in weight and BMI in both treatment groups, with a slightly larger decrease in the aliskiren compared to the enalapril treatment group. There was a greater LS mean increase from Baseline in height after 104 weeks (Week 156) in secondary hypertension patients compared to the increase observed after 52 weeks (Week 104) in primary hypertension patients, which is

					expected in these growing paediatric patients. Results of the neurocognitive assessments, performed only in patients with secondary hypertension, showed some improvements in most of the test scores, with no meaningful difference between the treatment groups.
IA/0121/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	18/05/2018	n/a		
IB/0120	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)	04/05/2018	20/09/2018	SmPC	
PSUSA/89/201709	Periodic Safety Update EU Single assessment - aliskiren, aliskiren / hydrochlorothiazide	12/04/2018	n/a		PRAC Recommendation - maintenance
IA/0118	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	19/01/2018	n/a		
WS/1026	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	14/12/2017	20/09/2018	SmPC	Study F2301 evaluated the effect of aliskiren as monotherapy and of the combination of aliskiren with enalapril compared to enalapril for cardiovascular mortality

	Update of section 5.1 of the SmPC in order to reflect the results of study SPP100F2301 (ATMOSPHERE) a multicenter, randomized, doubleblind, parallel group, active-controlled study to evaluate the efficacy and safety of both aliskiren monotherapy and aliskiren/enalapril combination therapy compared to enalapril monotherapy, on morbidity and mortality in patients with chronic heart failure (NYHA Class II - IV). The RMP (v 13.2) has also been updated to reflect the study results. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				and morbidity benefit in a double-blind active controlled randomised study in 7,064 patients with chronic heart failure (NYHA Class II-IV) and reduced left ventricular ejection fraction (LVEF ≤35%), of which 62% had a history of hypertension. The primary endpoint was a composite of cardiovascular death and first hospitalisation for heart failure. The final results of the study did not demonstrate statistically that aliskiren was non-inferior to enalapril on the primary endpoint; however, there was essentially no difference in the observed incidence rates between aliskiren and enalapril. There was no significant benefit of adding aliskiren to enalapril. Treatment effects were similar in patients with diabetes and with renal insufficiency. The incidence of adjudicated stroke was not significantly different between the aliskiren and enalapril groups or between the combination and enalapril groups. The incidence of adverse events tended to be higher in patients with diabetes, or with GFR <60 ml/min/1.73 m², or with age ≥ 65 years; however, there was no difference between patients treated with aliskiren and those treated with enalapril. The incidence of certain adverse events was similar between aliskiren and enalapril groups while there was an increased incidence of hyperkalaemia, renal impairment/renal failure and hypotension related events with the combination of aliskiren and enalapril. There was a statistically significant increased incidence of syncope with the combination of aliskiren and enalapril compared to enalapril in the overall population and in the subgroups NYHA I/II overall. The incidence of atrial fibrillation was 11.1%, 13.3%, and 11.0% in the combination, aliskiren, and enalapril groups,

					respectively. Statistically significantly higher incidences in the occurrence of cardiac failure and ischaemic stroke were also found for aliskiren compared to enalapril in patients with NYHA I/II with hypertension, and in the occurrence of chronic cardiac failure and ventricular extrasystole in patients with NYHA III/IV with hypertension. For the combination of aliskiren and enalapril there were statistically significant differences in the rate of angina unstable compared to enalapril. No clinically relevant differences in efficacy or safety results were observed in the subpopulation of elderly patients with a history of hypertension and chronic heart failure Class I-II compared to the overall study population.
IAIN/0116	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	12/10/2017	20/09/2018	Annex II and PL	
IB/0115	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/10/2017	20/09/2018	SmPC and PL	
T/0114	Transfer of Marketing Authorisation	21/07/2017	22/08/2017	SmPC, Labelling and PL	
R/0112	Renewal of the marketing authorisation.	23/03/2017	22/05/2017	SmPC, Annex II, Labelling and PL	
PSUSA/89/201609	Periodic Safety Update EU Single assessment - aliskiren, aliskiren / hydrochlorothiazide	05/05/2017	n/a		PRAC Recommendation - maintenance

IA/0111/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites	14/11/2016	n/a		
WS/0891	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, 5.1 and 5.2 of the SmPC for Rasilez and section 4.8, 5.1 and 5.2 of Rasilez HCT on the basis of the completed long term extended paediatric study CSPP100A2365E1. The MAH has taken the occasion to include some editorial changes in both SmPCs and to better summarise the information from non-clinical studies in section 5.3 of both SmPCs at the request of the CHMP. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	22/05/2017	SmPC	The safety and efficacy of Rasilez in children aged 6 to 17 years have not yet been established. Currently available data are described in sections 4.8, 5.1, and 5.2, but no recommendation on a posology can be made. Aliskiren has been evaluated for safety in a randomised, double-blind, 8-week study in 267 hypertensive patients aged 6 to 17 years, mostly overweight/obese, followed by an extension study including 208 patients treated for 52 weeks. This study was extended with a 52-week double-blind, randomised study to evaluate the safety, tolerability and efficacy of aliskiren compared to enalapril in 208 paediatric hypertensive patients aged 6 to 17 years (at baseline in the previous study). At the end of this extension study, changes in msSBP from baseline were similar with aliskiren compared to enalapril (7.63 mmHg vs. 7.94 mmHg) in the full analysis set. However, the significance of the non-inferiority testing was not maintained when the analysis was performed on the per-protocol set. In addition, due to the possibility of up-titration if medically necessary to control the msSBP, no conclusion can be

					drawn on the appropriate posology of aliskiren in patients aged 6 to 17 years. In the 8-week randomised, double-blind study with aliskiren monotherapy in 267 paediatric hypertensive patients aged 6 to 17 years, mostly overweight/obese, fasting trough aliskiren concentrations at day 28 were comparable to those observed in other studies in both adults and children using similar aliskiren doses. In juvenile repeated toxicity studies in rats aliskiren at 100 and 300 mg/kg/day was associated with high mortality and severe morbidity. Increased systemic exposure to aliskiren (>400-fold higher in 8 day old rats compared with adult rats) was observed. The MDR1 gene expression in juvenile rats was also significantly lower when compared to adult rats. The increased aliskiren exposure in juvenile rats appears to be attributed mainly to lack of maturation of P-gp. There is therefore a potential for aliskiren overexposure in paediatric patients with immature MDR1.
WS/0890	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of study SPP100A2417 "A multi-database cohort study to assess the incidence rates of colorectal hyperplasia among hypertensive patients". C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/09/2016	n/a		

WS/0771	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 (v 12.3) with regards to identified risks, missing information, concomitant use of other medicines, drug-drug interactions, removal of safety issues attributed to the now withdrawn aliskiren/amlodipine (Rasilamlo) and aliskiren/amlodipine/HCTZ (Rasitrio). 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	15/09/2016	22/05/2017	SmPC	The main changes to the RMP are the deletion of all information on the fixed association aliskiren/amlodipine (SPA100) and aliskiren/amlodipine/HCTZ in view of their withdrawal in the EU, the deletion of some risks and the deletion of the study ASSESS (CSPP100A2370) from the list of studies in post authorization development plan based on submission of the Study Report SPA100A "Antihypertensive Effects and Long-Term Safety of Ali in Elderly Patients".Section 5.1 of the SmPC has been also updated to reflect that in a pooled analysis of efficacy and safety data from clinical trials up to 12 months duration, there was no statistically significant difference in blood pressure reduction between aliskiren 300 mg and aliskiren 150 mg in elderly patients (≥ 65 years). The RMP has also been revised with this submission.
WS/0849	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, 4.5 and 5.2 of the SmPC in order to update information on food effect on administration of aliskiren as analysed in study SPP100A2413. The Package Leaflet is updated accordingly. In addition, the worksharing applicant (WSA) took the opportunity to bring the PI in line with the latest QRD template version 9.1. C.I.3.b - Change(s) in the SPC, Labelling or PL	26/05/2016	24/06/2016	SmPC, Annex II, Labelling and PL	The efficacy of aliskiren was shown to be similar when taken either with a light meal or without a meal. Oral use: The tablets should be swallowed whole with some water. Rasilez should be taken once a day, with or without food, preferably at the same time each day. Patients should establish a convenient daily schedule of drug intake and maintain a steady temporal relationship with food intake. Concomitant intake with fruit juice and/or drinks containing plant extracts (including herbal teas) should be avoided.

	intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				
PSUSA/89/20 1509	Periodic Safety Update EU Single assessment - aliskiren, aliskiren / hydrochlorothiazide	14/04/2016	n/a		PRAC Recommendation - maintenance
IG/0669/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	17/03/2016	n/a		
WS/0807	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	28/01/2016	n/a		
WS/0793	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.z - Change(s) in the SPC, Labelling or PL	14/01/2016	24/06/2016	SmPC	

	intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation				
WS/0799	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.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	14/01/2016	24/06/2016	SmPC	
IA/0105/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	10/12/2015	n/a		
PSUSA/89/201409	Periodic Safety Update EU Single assessment - aliskiren, aliskiren / hydrochlorothiazide	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/89/201409.
IA/0099/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/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	01/04/2015	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. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	n/a		
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	
IA/0098/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/importer of the	14/01/2015	n/a		

	finished product, including quality control sites (excluding manufacturer for batch release)				
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		
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	25/09/2014	n/a		N/A

	of studies to the competent authority				
A31/0085	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 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.	22/05/2014	04/09/2014	SmPC and PL	For further information please refer to the Renin-angiotensin-system (RAS)-acting agents Article 31 referral - Assessment report.
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.	20/02/2014	n/a		

	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				
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.	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

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				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	10/01/2014	n/a		

	of the AS				
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.
WS/0412	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	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 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.
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

	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).
IB/0083	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	21/06/2013	26/07/2013	PL	
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",	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

	"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-clinical, clinical or pharmacovigilance data				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.
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	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

	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/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	17/04/2013	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.
IB/0077/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	05/03/2013	n/a		

	procedure				
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/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.	13/12/2012	24/01/2013	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.

	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				
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	24/01/2013	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.	18/10/2012	22/11/2012	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

	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 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				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 assessment of FU2 026 for aliskiren and FU2 027 for aliskiren/HCTZ. Following the assessment of the data provided, additional amendments not related to the scope of the present procedure were implemented to correct some inconsistencies in the changes to the Product Information approved in the previous WS173 procedure for Rasilez HCT.

IG/0232	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	14/11/2012	n/a		
IA/0074/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.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	23/10/2012	n/a		
IG/0220/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	09/10/2012	n/a		

R/0062	Renewal of the marketing authorisation.	19/07/2012	23/08/2012	SmPC, Annex II, Labelling and PL	
IG/0209/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	17/08/2012	n/a		
IG/0206	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	23/07/2012	n/a		
IG/0196/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	13/07/2012	n/a		
WS/0189	This was an application for a variation following a worksharing procedure according to Article 20 of	19/04/2012	25/05/2012	SmPC	Aliskiren is mainly eliminated through the hepatobiliary route. Renal excretion only accounts for 0.6% of the

	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				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.
A20/0063	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	SmPC, Annex II and PL	Please refer to the Assessment Report: Rasilez-H-780-A20-63-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.	16/02/2012	16/02/2012		

	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				
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	20/10/2011	22/11/2011	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

	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				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	22/11/2011	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.
IG/0088/G	This was an application for a group of variations.	11/07/2011	n/a		

	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				
WS/0139/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To add a new manufacturing site, Novartis Grimsby Ltd, UK, for the intermediates of aliskiren, respectively C3 and C6. Together with this change, several changes have been introduced to the reagents, solvents, starting material specifications and batch size at the proposed site. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold	23/06/2011	23/06/2011		

	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/0098	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC to add the Adverse Drug Reaction 'hypersensitivity reactions' under post-marketing experience as requested by CHMP following PSUR review. The Package Leaflet	14/04/2011	23/05/2011	SmPC and PL	Following the review of PSUR 5 for aliskiren MAH was requested to consider updating the SmPC to add severe cutaneous adverse reactions (SCARs) and arthralgia. Conducted review of all cases of SCARs and of arthralgia did not demonstrate an evidence of a clear causal relationship between these events and aliskiren treatment. However, the analysis revealed a possible relationship between these events and hypersensitivity. Subsequently

	has been updated accordingly. In addition, the MAH takes the opportunity to update the contact details in the Package Leaflet of the local representative in Poland. This application was submitted for a group of variations consisting of Type II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				MAH has performed a detailed analysis of available data. The evidence presented is considered to support the inclusion of post-marketing events of "hypersensitivity" into the SmPC section 4.8 (undesirable effects) for aliskiren.
WS/0055	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.2 and 5.1 of the SmPC to include information about the efficacy and safety of aliskiren in elderly and very elderly hypertensive patients based on data from the AGELESS study. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	23/05/2011	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) hypertensive patients. Overall the results of this clinical study support the conclusion of a positive benefit/risk ratio in the use of the aliskiren+HCTZ as antihypertensive treatment of elderly and very elderly patients. However, the review of available data also suggests different response to the treatment of elderly and very elderly. As a result sections 4.2 and 5.1 have been updated by including information about the efficacy and safety of aliskiren in elderly and very elderly hypertensive patients.
II/0041	This type II variation concerned an update of section 4.3 of the Summary Product Characteristics (SmPC) to remove verapamil from the contraindications, and sections 4.4 and 4.5 of the SmPC, following the CHMP assessment of FUM 015 and FUM 017,	17/03/2011	18/04/2011	SmPC, Labelling 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 FUM 015 MAH

	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, the MAH took the opportunity to implement minor editorial changes in the annexes and to update the 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				was requested to provide additional preclinical data evaluating the potential mechanism of the ciclosporin and other potent P-gp inhibitor interaction with aliskiren. The MAH applied for a type II variation update section 4.3 of the SmPC to remove verapamil from the contraindications, and sections 4.4 and 4.5 of the SmPC, following the CHMP assessment of FUM 015 and FUM 017, regarding the potential for interaction of aliskiren with verapamil, and the impact of Pgp inhibition on the distribution of aliskiren. The proposed changes to the product information are acceptable.
WS/0073	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This type II variation concerns an update of sections 4.2 and 4.5 of the SPC in view of the results of study CSPP100A2112 investigating the potential interaction between aliskiren and grapefruit juice in healthy subjects. The Package Leaflet has been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/02/2011	18/03/2011	SmPC	This type II variation concerns an update of section 4.5 of the SPC in view of the results of study CSPP100A2112 investigating the potential interaction between aliskiren and grapefruit juice in healthy subjects. Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and Cmax of aliskiren. Co-administration with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with aliskiren. This application was submitted for a Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.
WS/0028	This was an application for a variation following a worksharing procedure according to Article 20 of	20/01/2011	21/02/2011	SmPC and PL	This type IB variation concerns an update of section 4.8 of the SPC, upon request by CHMP following the assessment

	Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics and Package Leaflet. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				of PSURs 4 and 5 for aliskiren, to add the ADR 'blood creatinine increase' under post-marketing experience. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make some minor editorial changes to the safety information already included in section 4.8 of the SPC. This application was submitted as a Type IB variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.
IB/0046/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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	27/01/2011	n/a		
WS/0069	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This type IB variation concerns an update of sections 4.3, 4.4 and 4.8 of the SPC, upon request by CHMP	16/12/2010	21/01/2011	SmPC	This type IB variation concerned an update of sections 4.3, 4.4 and 4.8 of the SPC, upon request by CHMP following a review by the PhVWP of the risk of angioedema with aliskiren, to add the new contraindication 'hereditary or idiopathic angioedema' and to add further information about the risk of angioedema with aliskiren administration.

	following a review by the PhVWP of the risk of angioedema with aliskiren, to add the new contraindication 'hereditary or idiopathic angioedema' and to add further information about the risk of angioedema with aliskiren administration. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				The application was submitted for a Type IB variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. See scientific discussion EMA/H/C/XXXX/WS/0069.
IG/0032/G	This was an application for a group of variations. To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 9.0, to include: - a change in the deputy of the Qualified Person for Pharmacovigilance (QPPV); - a change in the major contractual arrangements. - administrative changes not impacting the operation of the pharmacovigilance system. Annex II.B has also been updated with the latest wording as per October 2010 CHMP procedural announcement. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the	21/12/2010	n/a		

	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				
WS/0037	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics, Annex II and Package Leaflet C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/09/2010	03/11/2010	SmPC, Annex II and PL	This type II variation concerned an update of section 4.3 of the SPC to add a contraindication for the concomitant use of aliskiren and itraconazole, and section 4.5 of the SPC to add information regarding this interaction following the publication of a study in healthy subjects. The Package Leaflet has been updated accordingly. A study in healthy volunteers showed that itraconazole (100 mg) increases AUC and Cmax of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and the potent P-gp inhibitor itraconazole is contraindicated. In addition, the MAH took the opportunity to update the annexes in line with the latest QRD template (version 7.3). This application was submitted for a Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. See scientific discussion EMA/H/C/xxx/WS/0037.
II/0042	This type II variation concerned an update of section 4.8 of the SPC, upon request by CHMP following the assessment of PSUR 3 and PSUR 4 for Rasilez (aliskiren), to include information about the ADR 'peripheral oedema'. The Package Leaflet has been	22/04/2010	02/06/2010	SmPC and PL	Peripheral oedema has been reported with aliskiren use in the post-marketing setting. The detailed analysis of spontaneous reports showed that many cases were confounded by patient medical history or suspect concomitant medication. Nevertheless, a number of cases

	updated accordingly. 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				showed a positive dechallenge such that a causal relationship to treatment could not be excluded. Therefore, based on this analysis, and in accordance with CHMP's requests following assessment of PSUR 3 and PSUR 4 for Rasilez (aliskiren), the MAH applied for a type II variation to update the 'Undesirable effects' section of the SPC to add the text: "Post marketing experience: peripheral oedema (frequency unknown)". The Package Leaflet has also been updated accordingly. The proposed changes to the product information are acceptable and the benefit/risk balance remains unchanged.
IB/0044	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	23/04/2010	n/a		
IB/0043	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	23/04/2010	n/a		
IA/0045	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	13/04/2010	n/a		
II/0040	Update of the Detailed Description of the Pharmacovigilance system (DDPS).	18/02/2010	30/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (core version 8.0 and product specific version 6.0) in accordance with the current Pharmacovigilance guideline.

	Update of DDPS (Pharmacovigilance)				After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.
II/0036	Addition of an alternative container closure system (PCTFE/PVC blister) for Rasilez 150 mg and 300 mg film-coated tablets. New presentation(s)	19/11/2009	03/12/2009	SmPC, Labelling and PL	
IA/0039	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	24/07/2009	n/a		
IA/0038	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	24/07/2009	n/a		
IA/0037	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	24/07/2009	n/a		
II/0035	Update of SPC section 5.1 to delete the existing sentence relating to elevated plasma renin activity and cardiovascular outcomes. Update of Summary of Product Characteristics	19/03/2009	22/04/2009	SmPC	The following sentence has been deleted from SPC section 5.1 based on the fact that currently no data are available to directly link the reduction in renin activity induced by aliskiren with effects on cardiovascular outcomes: "Elevated PRA has been independently associated with increased cardiovascular risk in hypertensive and normotensive patients." as currently there is no evidence available proving that changes in renin activity induced by antihypertensive drugs might have an important role in cardiovascular disease.
II/0034	Update of SPC section 4.4 to include a warning of events of renal dysfunction in at-risk patients and to amend the existing text for renal artery stenosis	19/02/2009	03/04/2009	SmPC and PL	For aliskiren, cases of renal dysfunction with relevant occurrence were reported in the postmarketing use (PSUR 1 and PSUR 2).

	following the CHMP assessment of PSURs. SPC section 4.8 has been updated relating to events of renal dysfunction and acute renal failure during post-marketing experience. The package leafet has been amended accordingly. Update of Summary of Product Characteristics and Package Leaflet				Following evaluation of the available postmarketing data, the CHMP concluded to add a warning to SPC section 4.4 that caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolemia (eg. due to blood loss, severe or prolonged diarrhea, prolonged vomiting, etc.), heart disease, liver disease or kidney disease. Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience.. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued. Furthermore, SPC section 4.8 was also amended.
II/0033	Update of SPC section 4.5 to include a statement regarding the potential interaction with non-steroidal anti-inflammatory agents (NSAIDs). The package leaflet has been amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	03/04/2009	SmPC and PL	The MAH was requested to add a statement regarding the potential for interaction between NSAID's and agents acting on the Renin Angiotensin System to SPC section 4.5. As with other agents acting on the renin -angiotensin system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination of aliskiren with an NSAID requires caution, especially in elderly patients. The package leaflet has been amended accordingly.
II/0032	Update of SPC sections 4.3 and 4.4 to include a contraindication on the use in patients with prior history of angioedema and a warning of angioedema-type reactions as for other agents acting on the renin-angiotensin system respectively, following the	19/02/2009	03/04/2009	SmPC and PL	For aliskiren, cases of angioedema with relevant occurrence were reported in the postmarketing use. Following the assessment of the available data, the CHMP concluded that a contraindication for patients with a history of angioedema with aliskiren is needed. In addition, a warning of

	CHMP assessment of PSURs. Furthermore, SPC section 4.8 has been revised regarding angioedema cases and the Package Leaflet has been updated in accordance with the SPC changes. Update of Summary of Product Characteristics and Package Leaflet				angioedema-type reactions as for other agents acting on the renin-angiotensin system has been added to SPC section 4.4 recommending that patients without a previous history who suffer angioedema with aliskiren should discontinue treatment and contact their doctor. Furthermore,the term "angioedema" has been added as a rare adverse drug reaction to SPC section 4.8.
II/0031	Update of or change(s) to the pharmaceutical documentation	25/09/2008	02/10/2008		
II/0026	Update of SPC section 4.3 "Contraindications" and section 4.5 "Interactions" following new information from a cyclosporine drug-drug interaction study (SPP100A2106), which was subject to a Follow-Up Measure. Further revisions were introduced to section SPC sections 4.4 "Warnings and Precautions for use" and 4.5. The package leaflet has been amended accordingly. In addition, minor corrections have been included in the relevant sections of SPC, labelling and package leaflet with regard to the active substance (aliskiren hemifumarate) and also for PL section 5. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/07/2008	28/08/2008	SmPC, Labelling and PL	The results of the cyclosporine interaction study in 14 subjects showed that concomitant cyclosporine administration increased AUC 4.5 to 5.5 fold with a lower dose of aliskiren (75 mg) than the authorised strengths (150 and 300mg). Also cyclosporine markedly increased aliskiren t1/2. Hence, there is concern that the increase in AUC would be substantially higher with the approved aliskiren dosage, even exceeding the highest dose tested in humans. An additional concern is that aliskiren might distribute to tissues from which the medicinal product is normally absent in presence of a P-gp inhibitor, or preset at low levels because of the activity of P-gp. Non clinical and clinical data converge to show that P-gp is a major determinant of aliskiren bioavailability. In addition, literature data show that P-gp mediates tissue uptake of a variety of P-gp substrates and that P-gp inhibitors can markedly increase the tissue-to-plasma concentration ratios. Given the very limited safety data at increased exposure,

					and the risk for very large increase in tissue exposure, the CHMP concluded that the co-administration of cyclosporine and aliskiren poses serious safety concerns. Therefore, a contraindication for the concomitant administration with cyclosporine, a highly potent P-gp inhibitor, as well as with other potent P g inhibitors (verapamil, quinidine) is considered essential. Moreover, due to the risk for higher increase in tissue exposure than in plasma, caution should be advised during co administration with moderate P-gp inhibitors (ketoconazol, itraconazol, clarithromycin, telithromycin, erythromycin, amiodarone).
II/0029	Update of SPC section 5.1 "Pharmacodynamic Properties" with efficacy data from a clinical study (study SPP100C2201) in patients with nephropathy. Update of Summary of Product Characteristics	30/05/2008	09/07/2008	SmPC	Study SPP100C2201, a 6 monthly randomised, double-blind, placebo-controlled study investigated the effects of aliskiren (150mg / 300mg) on proteinuria in 599 patients with hypertension and Type II 2 diabetes mellitus in whom blood pressure had been previously controlled by means of an angiotensin receptor blocker (losartan) in combination with the optional use of other antihypertensive drugs (hydrochlorothiazide and/or amlodipine). The addition of 300mg aliskiren achieved an average reduction in the urinary albumin to creatinine (UACR) ratio of 12 mg/mmol (from 58 to 46 mg/mmol) compared to placebo. Aliskiren did not induce any significant effect on blood pressure or affect estimated GFR under these conditions. The clinical relevance of a reduction in UACR is not established in the absence of an effect on blood pressure. Furthermore, aliskiren was associated with an increased frequency (4.2% vs. 1.9% for placebo) in serum potassium concentration (? 6 mmol/l).
II/0028	Update of the SPC section 4.4 and 5.1 following new	30/05/2008	09/07/2008	SmPC	Study SPP100A2313, a 12-week double-blind, randomised,

	information from a study (SPP100A2313) in patients with heart failure. Update of Summary of Product Characteristics				placebo-controlled, 2-arm study of aliskiren 150 mg od added to standard therapy in patients with stable heart failure evaluated the overall safety and tolerability of aliskiren 150 mg when given in addition to standard therapy in hypertensive patients with stable heart failure. The study included 302 patients with mild to moderate heart failure. Addition of 150 mg aliskiren showed a reduction of BNP levels by 25 %, although the clinical significance of this reduction is unknown. No statistically significant differences in signs and symptoms of heart failure were found and overall grading of patients according to NYHA classification remained unchanged.
II/0030	Update of or change(s) to the pharmaceutical documentation	30/05/2008	11/06/2008		
IB/0012	IB_10_Minor change in the manufacturing process of the active substance IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	31/01/2008	n/a		
IA/0027	IA_32_a_Change in batch size of the finished product - up to 10-fold	18/01/2008	n/a		
IB/0023	IB_33_Minor change in the manufacture of the finished product	04/01/2008	n/a		
IB/0022	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	04/01/2008	n/a		

IA/0024	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	23/11/2007	n/a		
IB/0002	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	15/11/2007	n/a		
IB/0001	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	15/11/2007	n/a		
IA/0020	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		
IA/0019	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		
IA/0018	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		
IA/0017	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		
IA/0016	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		
IA/0015	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		
IA/0014	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		

IA/0013	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/11/2007	n/a		