EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Riprazo HCT

Procedural steps taken and scientific information after the authorisation

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2]/ amended on	Product Information affected[3]	Summary
IG/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/0201/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	24/07/2012	n/a		

[1] Notifications are issued for type I variations (unless part of a group or a worksharing application). Opinions are issued for all other procedures.
[2] No Commission Decision is issued for type IA and type IB variations or for type II variations and annual re-assessments that do not affect the annexes.
[3] SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	or addition of a site where batch control/testing takes place, 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.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				
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		

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WS/0173	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	28/06/2012	SPC, PL	The MAH has undertaken the following in-depth review of the clinical safety and clinical pharmacology information available to date on the HCTZ component of the fixed-dose combination: Review of Esidrex (containing HCTZ, first authorised in Switzerland in 1958, nationally authorised in 39 countries) PSURs 1-6 (1 Oct 1989-31 Dec 2009); Cases/events from the MAHs Global Safety Database (NGSD): NGSD was reviewed cumulatively (cut-off date 13 Apr 2010) for all cases (spontaneous reports including literature reports as well as serious adverse events from clinical trials) to identify any unlisted event clusters for Esidrex. No new unlisted event cluster was identified in the summary tabulation from the safety database search; Literature review: Major drug reference books, including Martindale (HCTZ) and Meyler's side effects (thiazide diuretics), were reviewed for unlisted adverse reactions, and bridging literature searches up to the cut-off date of 13 Apr 2010 were performed as per PSUR search criteria (publication date from the PSUR 6 cut-off date: 31 Dec 2009). As a consequence, sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Section 4.4 of the SmPC has been updated to include a new warning on the potential risk of 'acute angle-closure glaucoma' associated with the use of hydrochlorothiazide. Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to a week of treatment initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue

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					hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulphonamide or penicillin allergy. As further major changes to section 4.8 of the SmPC the following new ADRs have been added: asthenia, pyrexia, erythema multiforme, aplastic anaemia, acute renal failure, muscle spasm and acute angle-closure glaucoma. Section 4.3 of the SmPC has been updated to add hyponatraemia and symptomatic hyperuricaemia to the contraindications.
WS/0189	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/04/2012	25/05/2012	SPC	Aliskiren is mainly eliminated through the hepatobiliary route. Renal excretion only accounts for 0.6% of the administered dose. No adjustment of the initial dosage is required in patients with mild to severe renal impairment, however caution should be exercised in patients with severe renal impairment. The MAH has conducted a study (Study SPP100A2262) to characterize the pharmacokinetics and safety of aliskiren in End-Stage Renal Disease (ESRD) patients receiving haemodialysis (HD). It is concluded that no dose adjustment is needed in patients with ESRD. A novel and important finding of the study is that aliskiren cannot be efficiently removed by HD. Based on the data of Study SPP100A2262, the MAH proposes to change the section 4.9 and 5.2 of the SmPC.
A20/0015	Article 20 Review On 20 December 2010, the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004 for all aliskiren-containing medicinal products authorised in the centralised procedure and requested	16/02/2012	20/04/2012	SPC, Annex II, PL	Please refer to the Assessment Report: Riprazo HCT-H-2420-A20-15-Assessment Report-Article 20.

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	the CHMP to assess all the available data and its impact on the risk benefit balance for aliskiren-containing medicinal products and to give its opinion on whether the marketing authorisations for these products should be maintained, varied, suspended or revoked. The scope of the review was to assess the risk benefit balance of all aliskiren-containing medicinal products in the approved indication of hypertension in light of the emerging safety data from the ALTITUDE study in patients with diabetes at high risk for cardiovascular and renal events which lead to the premature study termination. Article 20 Review				
IG/0148/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	22/02/201	n/a		

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

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	a starting material/intermediate				
WS/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 A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	20/10/2011	22/11/2011	SPC, PL	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,	20/10/2011	22/11/2011	SPC, PL	Toxic epidermal necrolysis (TEN) is considered severe cutaneous adverse reaction (SCAR) as it is severe, unpredictable, and drug-induced. TEN is characterized by extensive detachment of the epidermis and erosions of the mucous membranes. In response to request from CHMP, the MAH has conducted comprehensive review in which cases of SCARs have been identified where the causal relationship with aliskiren cannot be ruled out in

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	following the assessment of PSUR 5. The MAH has submitted consequential changes to the Package Leaflet. In addition, minor changes have been made in the Section 2 of the Package Leaflet with regards to angioedema for Rasilez, Rasilez HCT, Riprazo and Sprimeo. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				the absence of alternative explanations. Considering the severity of the described reactions, the CHMP requested "SCARS" including "TEN" and "oral mucosal reactions" to be added in section 4.8 of aliskiren containing product SmPC.
WS/0169	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.3 of the Summary Product Characteristics (SmPC) to remove verapamil from the contraindications, and sections 4.4 and 4.5 of the SmPC, following the CHMP assessment of the data regarding the potential for interaction of aliskiren with verapamil, and the impact of P-gp inhibition on the distribution of aliskiren. The Package Leaflet has been updated accordingly. In addition, MAH took opportunity to update the contact details of local representatives in the PIL for Riprazo, Sprimeo and Riprazo HCT. This application is submitted in	22/09/2011	27/10/2011	SPC, PL	Contraindication with regards to concomitant use of aliskiren and the highly potent P-gp inhibitor ciclosporin and other potent P-gp inhibitors (verapamil, quinidine) was introduced on the basis of results from drug-drug interaction study. Subsequently, as a part of Rasilez FUM 015 MAH was requested to provide additional preclinical data evaluating the potential mechanism of the ciclosporin and other potent P-gp inhibitor interaction with aliskiren. A type II variation was approved to remove the contraindication against concomitant use of verapamil and aliskiren from the Summary of Product Characteristics of Rasilez and RasilezHCT (II/41 and II/05-G, approved in March 2011) and to include a statement with regard to potential for interaction with organic anionic transporting polypeptide (OATP) inhibitors and with rifampicin. Corresponding amendments were also introduced into the Patient leaflet. The present variation application is submitted to introduce the same changes to the Product Information

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	fulfilment of the FUM001 for Riprazo HCT and Sprimeo HCT. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				for all aliskiren-containing medicinal products. The proposed changes to the product information are acceptable. See Scientific Discussion: EMA/H/C/xxx/WS/0169.
WS/0165	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 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	22/09/2011	27/10/2011	SPC	AGELESS study was conducted in order to specifically evaluate the safety and efficacy of aliskiren and aliskiren/HCT in elderly (>65ys) and very elderly (>75 ys) hypertensive patients. Overall the results of this clinical study support the conclusion of a positive benefit/risk ratio in the use of the aliskiren+HCTZ as antihypertensive treatment of elderly and very elderly patients. However, the review of available data also suggests different response to the treatment of elderly and very elderly 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.
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	22/09/2011	27/10/2011	SPC, 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

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	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				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-	22/09/2011	27/10/2011	SPC	

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	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				
IG/0101	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	18/08/2011	n/a		
IG/0102	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	18/08/2011	n/a		
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/07/2011	n/a	PL	
IG/0088/G	This was an application for a group of variations. C.I.9.e - Changes to an existing	11/07/2011	n/a		

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	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				