22 September 2011
EMA/CHMP/479606/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sprimeo, Riprazo (aliskiren),
Rasilamlo (aliskiren/amlodipine),
Riprazo HCT, Sprimeo HCT (aliskiren / hydrochlorothiazide)

Procedure No.: EMEA/H/C/xxx/WS/0169

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

Aliskiren is an anti-hypertensive agent, which acts by inhibiting the enzyme renin to block the conversion of angiotensinogen to angiotensin I, the precursor of angiotensin II. Aliskiren (Rasilez) at once daily doses of 150 and 300 mg was approved in the EU on 22 August 2007, for use as monotherapy, or in combination with other anti-hypertensive agents, for the treatment of mild to moderate hypertension.

On 13 April 2011, the fixed dose combination aliskiren/hydrochlorothiazide (RiprazoHCT), was authorised in the EU for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone, and as substitution therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination. The approved dosages are: 150/12.5 mg, 150/25 mg, 300/12.5 mg, 300/25 mg.

Rasilamlo, the fixed dose combination of aliskiren and amlodipine (150/5mg; 150/10mg; 300/5 mg 300/10mg) was authorised in the EU on 14 April 2011 for the treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled with aliskiren or amlodipine used alone.

A type II variation was approved to remove the contraindication against concomitant use of verapamil and aliskiren from the Summary of Product Characteristics of Rasilez and RasilezHCT (II/41 and II/05-G, approved in March 2011) and to include a statement with regard to potential for interaction with organic anionic transporting polypeptide (OATP) inhibitors and with rifampicin. Corresponding amendments were also introduced into the Patient leaflet. The present variation application is submitted to introduce the same changes to the Product Information for all aliskiren-containing medicinal products.

The rationale for the removal of the verapamil contraindication was based largely upon the results of clinical study CSPP100A2111, herein assessed.

Based on preclinical data, it is known that P-gp is a major determinant of aliskiren bioavailability. A number of interactions studies have been conducted between aliskiren and inhibitors of P-gp, including cyclosporine, ketoconazole and atorvastatin and the results are described in the SmPC. The clinical study CSPP100A2111 was conducted to explore the pharmacokinetic interaction between aliskiren and verapamil in healthy volunteers. The results of the study were submitted to CHMP as a follow up measure for Rasilez in April 2009.

With this variation the MAH is fulfilling the FUM001 for RiprazoHCT and SprimeoHCT.

The changes to the PI as proposed by the MAH in section 9 of this AR and are identical to those approved for Rasilez and RasilezHCT:

The original assessment of variation II/41 and II/05 is reported below, including all evaluation waves.

On 24 July 2008, the Variation Application Rasilez II/26 was approved by the CHMP in order to update the SmPC on the basis of results from a recently completed drug-drug interaction study with

ciclosporin A (SPP100A2106). During the assessment the CHMP requested a contraindication with regard to concomitant use of aliskiren and the highly potent P-gp inhibitor ciclosporin and other potent P-gp inhibitors (verapamil, quinidine). Further revisions have been also introduced related to SmPC section 4.4 and the re-structuring of section 4.5. However, the adoption was accompanied by a list of follow-up measures to be fulfilled post-authorisation. Among these, FUM 015 (non clinical) was the following:

"To provide additional preclinical data evaluating the potential mechanism of the ciclosporin interaction with aliskiren. If the interaction with ciclosporin cannot be attributed to P-gp only, further investigation of transporters will be carried out.

The pre-clinical studies should clarify the effect of P-gp inhibition on aliskiren PK, including tissue distribution. Because the effect of ciclosporin may also be mediated by mechanisms other than P-gp inhibition, non clinical data on aliskiren tissue distribution in experimental models in which P-gp is absent (as the mdr-deficient mice) should be provided. The mechanism by which ciclosporin and other Pgp inhibitors inhibit aliskiren clearance may be investigated by using the same model (i.e., by investigating the effect of ciclosporin both in the mdr-deficient and wild-type mice)".

The MAH had already provided the study report of the pre-clinical study (DMPK R0700870: Distribution of SPP100 after single oral administration (15 mg free base/kg) of SPP100 hemifumarate to rats with or without co-administration of ciclosporin A") required by the Follow Up Measure 016: "To conduct a study to investigate the effect of P-gp on the tissue distribution of aliskiren".

The MAH subsequently submitted the data of the non clinical study "*Pharmacokinetics and tissue distribution after oral administration of 100 mg/kg aliskiren to mdr1a/1b deficient and wild type mice - Effect of ciclosporin and ketoconazole (DMPK R0900355)"* (for conclusive fulfilment of FUM 015). Based on the data of this study, the MAH proposed to eliminate the Contraindication (SmPC 4.3) for the concomitant use of aliskiren + verapamil and to add a Special warning (SmPC 4.4) for the concomitant use. In addition, the MAH proposed to amend the text of Section 4.4. and 4.5 in order to reflect the potential for interaction of aliskiren with verapamil, and the impact of Pgp inhibition on the distribution of aliskiren. The proposed variation applied to both aliskiren (Rasilez) and aliskiren/HCTZ (Rasilez HCT) product information (see concomitant RasilezHCT II/05 AR).

The Rapporteur considered that the variation could be approvable provided that the MAH adequately addressed the 2nd Request of Supplementary Information, which was the following: *"Available data convincingly demonstrate that P-gp inhibitors do not increase aliskiren distribution to the brain. Yet, these data do not allow to clarify whether or not verapamil may cause an increase in aliskiren distribution to tissues, and particularly those from which aliskiren is normally excluded. Therefore, available non clinical and clinical data may not be sufficiently predictive of toxicity arising from the presence of aliskiren in these tissues, when aliskiren is co-administered with verapamil. The MAH should consider performing a non clinical study investigating the effect of verapamil on the distribution of aliskiren to all the organs and tissues examined in a thorough distribution study and address the possible toxicological consequences of an altered distribution".*

The MAH has not performed any further study but has provided a response based on the discussion on previously submitted data and literature data.

This application concerns the following medicinal products:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Sprimeo	aliskiren	See Annex A

Medicinal product:	International non-proprietary name:	Presentations:
Rasilamlo	aliskiren / amlodipine	See Annex A
Riprazo	aliskiren	See Annex A
Riprazo HCT	aliskiren / hydrochlorothiazide	See Annex A
Sprimeo HCT	aliskiren / hydrochlorothiazide	See Annex A

The variations submitted in the group are the following:

Variation(s) requested		Type
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

This type II variation relates to the following changes:

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 Pgp inhibition on the distribution of aliskiren. The Package Leaflet has been updated accordingly. In addition, MAH took opportunity to update the contact details of local representatives in the PIL for Riprazo, Sprimeo and Riprazo HCT. This application is submitted in fulfilment of the FUM001 for Riprazo HCT and Sprimeo HCT.

1.2. Non-clinical aspects

Rationale for proposed changes

Non clinical data showed that PSC833 (an inhibitor of Mdr1 and Mrp2) dramatically decreased biliary clearance of aliskiren. The results of the ciclosporin-aliskiren drug-drug interaction study in healthy subjects showed that ciclosporin markedly increased aliskiren AUC while decreasing its clearance. Taken together these data suggest that P-gp is a major determinant of aliskiren absorption and elimination.

However, the effect of ciclosporin may also be due to the inhibition of liver uptake transporters. Therefore, the CHMP's evaluation was that a DDI study with verapamil would help clarifying the effects of P-gp inhibitors on aliskiren PK. The MAH provided the results of a DDI study with verapamil at steady-state. These data showed that verapamil increased aliskiren Cmax and AUC by ~2-fold. The effect of verapamil was consistent with that of other moderate P-gp inhibitors, ketoconazole (which increased aliskiren steady-state Cmax and AUC by ~80%) and atorvastatin (50% increase in aliskiren Cmax and AUC).

Yet, the contraindication for the co-administration with potent P-gp inhibitors such as verapamil was mainly based on concerns about the possible enhancement of tissue penetration due to P-gp inhibition.

A first non clinical study was submitted by the MAH with the aim of clarifying the effect of ciclosporin on distribution to tissues and particularly to the brain, from which aliskiren is normally excluded (study DMPK R0700870: *Distribution of SPP100 after single oral administration (15 mg free base/kg) of SPP100 hemifumarate to rats with or without co-administration of ciclosporin A",* required by the FUM 016). The study was carried out in rats. The results of the study showed that when ciclosporin was co-administered with aliskiren, the drug distributed to all tissues (but not to brain and spinal chord) from which it is normally excluded (after a single dose), such as bone marrow, eye (choroid), thyroid gland.

Notably, ciclosporin only caused a 2-fold increase in blood levels but a much greater increase in several tissues (~100-fold in liver, ~10-fold in kidney, ~20-fold in salivary gland). The increase of the tissue/blood ratios of concentrations suggested that ciclosporin inhibits a transporter-mediated efflux of aliskiren. Yet, this transporter has not been identified and the mechanism of the increase in exposure elicited by ciclosporin is still unknown. Moreover, the absence of aliskiren in the brain in the ciclosporin group could be due to too low ciclosporin concentrations at the blood brain barrier, as a consequence of the administration route chosen (oral administration).

The MAH has now submitted the results of a study carried out using the *mdr*-deficient mice model in order to clarify:

1) the effect of P-gp inhibition on tissue distribution, particularly to the brain;

2) whether the effect of ciclosporin is due only to P-gp inhibition or may involve other mechanisms. The effect of ketoconazole on aliskiren PK in wild type and P-gp knockout mice was also investigated.

Data submitted

Study DMPK R0900355

Wild type mice (WT) and P-gp knockout mice (KO) were orally dosed with aliskiren (100 mg/kg). The effect of co-administration of ciclosporin (p.o. and i.v.) and ketoconazole (p.o.) was also investigated both in WT and KO mice.

Treatment groups were the following:

A: mdr1a/1b (-/-) mice, 100 mg/kg p.o. aliskiren and pre-administration of Neoral vehicle microemulsion (4 mL/kg p.o.)

B: wild type mice, 100 mg/kg p.o. aliskiren and pre-administration of Neoral vehicle microemulsion (4 mL/kg p.o.)

C: mdr1a/1b (-/-) mice, 100 mg/kg p.o. aliskiren and pre-administration of ciclosporin (10 mg/kg p.o.)

D: wild type mice, 100 mg/kg p.o. aliskiren and pre-administration of ciclosporin (10 mg/kg p.o.)

E: mdr1a/1b (-/-) mice, 100 mg/kg p.o. aliskiren and pre-administration of ketoconazole (50 mg/kg p.o.)

F: wild type mice, 100 mg/kg p.o. aliskiren and pre-administration of ketoconazole (50 mg/kg p.o.)

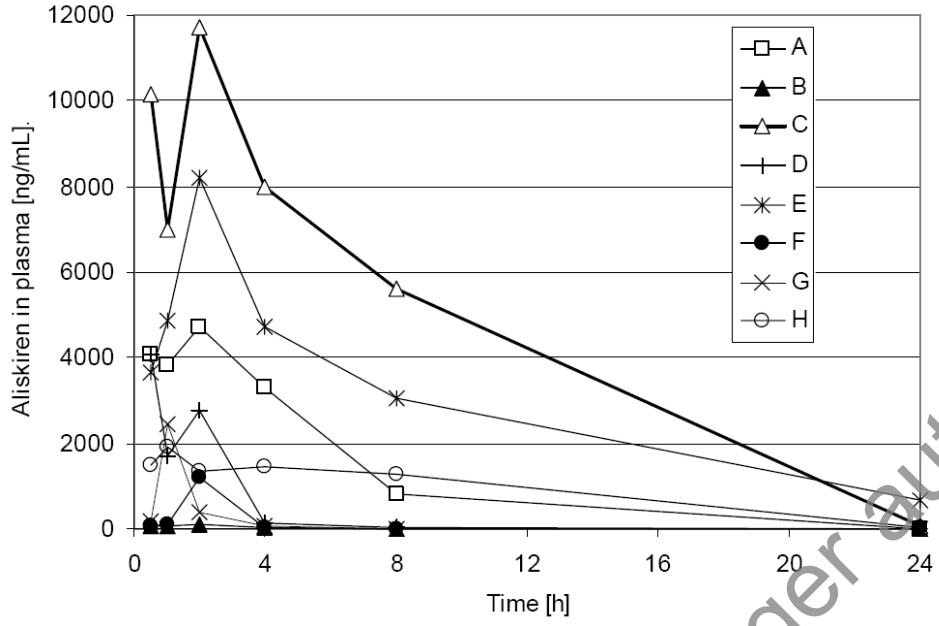
G: wild type mice, 100 mg/kg p.o. aliskiren and pre-administration of ciclosporin (5 mg/kg i.v.)

H: mdr1a/1b (-/-) mice, 100 mg/kg aliskiren and pre-administration of ciclosporin (5 mg/kg i.v.)

Test compound as well the inhibitor compounds were administered orally by gavage. Co-administration of vehicle or (inhibitor) compound solution was done 30 min before administration of the aliskiren solution. The doses of ciclosporin and ketoconazole were those previously used in published DDI studies. Each group included 12 animals (2 per time point). The sampling times for blood/plasma and organs/tissues were: 0.5, 1, 2, 4, 8 and 24h. The following tissues were dissected and analysed for aliskiren concentration: liver, kidney, brain, fat, muscle, lung and heart. Concentrations of aliskiren in plasma and tissues were determined by a quantitative LC/MS/MS method with a limit of quantification of 0.200 ng/mL.

Results

Plasma. Concentration-time curves of aliskiren in the 8 treatment groups are shown in the following figure:



PK parameters are shown in the following table:

	A	B	C	D	E	F	G	H
Cmax [ng/mL] *	4725	107	11725	4100	8215	1205	2453	1905
Tmax [h] *	2	2	2	0.5	2	2	1	1
AUC0-24h [h·ng/mL] *	30132	487	108687	8416	67630	2110	2961	21545

Legend: A: KO + vehicle; B: WT + vehicle; C: KO + p.o. Cyc; D: WT + p.o. Cyc; E: KO + p.o. Ket; F: WT + p.o. Ket; G: WT + i.v. Cyc; H: KO + i.v. Cyc. (Cyc: ciclosporin; Ket: ketoconazole).

Compared to WT mice, aliskiren AUC increased by 62-fold in KO mice (A *vs.* B).

Oral ciclosporin increased AUC by 17-fold in WT mice (D *vs.* B) and by 3.6 fold in KO mice (C *vs.* A). Intravenous ciclosporin also increased AUC by 6-fold in WT mice (G *vs.* B) but decreased AUC and Cmax in KO mice (H *vs.* A). Ketoconazole increased AUC by approx. 4 fold in WT mice (F *vs.* B) and by approx. 2 fold in KO mice.

Tissue levels

Brain

Aliskiren levels in brain are shown in the following table:

	Aliskiren in brain [ng/g] in treatment groups							
Time [h]	A	B	C	D	E	F	G	H
0.5	63.0	172	182	27.4	33.9	65.8	5.64	58.9
0.5	63.2	124	70.5	16.5	84.4	50.4	5.19	81.9
Mean	63.1	148	126	21.95	59.2	58.1	5.42	70.4
1	95.0	3.21	47.3	13.4	136	10.3	7.64	134
1	93.5	3.17	114	7.85	77.6	5.48	91.2	88.9
Mean	94.3	3.19	80.7	10.6	107	7.89	49.4	111
2	436	13.3	344	21.2	344	15.9	54	101
2	161	75	87.8	18.2	647	12.9	195	163
Mean	299	44.2	216	19.7	496	14.4	125	132
4	230	39	280	11.7	617	11.6	24.2	430
4	434	13.7	292	23.0	335	21.3	11.6	318
Mean	332	26.4	286	17.4	476	16.5	17.9	374
8	433	5.99	507	11.8	567	11.8	0	494
8	510	6.18	458	13.3	640	11.9	8.04	540
Mean	472	6.09	483	12.6	604	11.9	4.02	517
24	451	7.18	559	14.9	962	7.98	7.74	648
24	401	10.8	536	10.7	739	9.06	17.2	688
Mean	426	8.99	548	12.8	851	8.52	12.5	668
Cmax [ng/g] *	472	148	548	22.0	851	58.1	125	668
Tmax [h] *	8	0.5	24	0.5	24	0.5	2	24
AUC0-24h [h·ng/g] *	9653	317	10479	323	15105	278	419	11935
AUCbrain/ AUCplasma	0.32	0.73	0.10	0.04	0.22	0.14	0.14	0.55

* Calculated from the means

Legend: A: KO + vehicle; B: WT + vehicle; C: KO + p.o. Cyc; D: WT + p.o. Cyc; E: KO + p.o. Ket; F: WT + p.o. Ket; G: WT + i.v. Cyc; H: KO + i.v. Cyc.

In KO mice aliskiren levels are 30-fold higher than in WT mice (A vs. B). However, the AUCbrain/AUCplasma ratio is lower in KO than in WT mice (0.3 vs. 0.73), which may suggest that the higher levels in KO mice may be a consequence of the much higher plasma levels (62 fold higher in KO than in WT mice). On the other hand, in WT mice, brain levels were essentially unaffected by ciclosporin (both p.o. and i.v.) or ketoconazole, even though plasma levels were increased by both compounds (17 fold by ciclosporin).

P-gp inhibitors apparently do not increase the drug distribution to the brain, which suggests that the concentration of inhibitors at the blood-brain barrier may be too low to inhibit P-gp activity at this site. Accordingly, ciclosporin did not increase brain levels in KO mice.

Other tissues

In all other tissues aliskiren levels were 3 to 10 fold higher in KO than in WT mice. These differences appear to be due to the increase in plasma levels because the Tissue/Plasma AUC ratios were all lower in KO than in WT mice. In the table below Tissue/Plasma AUC ratios are shown for WT and KO mice.

Tissue	WT mice	KO mice
Liver	44	5
Kidney	34	4
Lung	11	0.6
Fat	5.7	0.3
Heart	4.8	0.8
Muscle	3.8	0.4
Brain	0.73	0.3

In WT mice, co-administration of ciclosporin caused a 2-3 fold increase in aliskiren levels in kidney, heart and lung, and a decrease in the tissue/plasma AUC ratio.

In liver, levels were lower in mice co-treated with oral, but not intravenous, ciclosporin with respect to control WT mice. The difference is essentially due to a marked difference in 0.5 h levels (control mice: 23,550 ng/g; oral ciclosporin treated mice: 3,745 ng/g). The underlying mechanism is unknown but it appears possible that ciclosporin may inhibit hepatic uptake of aliskiren. Ciclosporin also decreased liver levels in KO mice, which indicates that the effect is independent of P-gp inhibition.

In WT mice, co-administration of ketoconazole did not cause changes in aliskiren tissue levels, with respect to control mice. The tissue/plasma AUC ratio was consequently lower in all tissues.

Overall conclusions

The non clinical data provided by the MAH convincingly demonstrate that the original safety concern which led to classify verapamil as a potent P-gp inhibitor is not supported by experimental data. In rats, the increase caused by verapamil in the tissue levels of the prototype P-gp substrate, digoxin, was very similar to the increase in plasma levels.

Therefore, the contraindication for the concomitant administration of verapamil and aliskiren can be removed. A warning should be added in section 4.4 of SmPC (under subheading 'Moderate P-gp inhibitors).

The Risk Management Plan has been updated accordingly.

Clinical and non clinical data indicate that the role of P-gp and other transporters in aliskiren PK is more complex than that described in the current SmPC. In particular, as noted by the Novartis scientific team, aliskiren is also a substrate for OATP2B1-mediated transport in vitro, and OATP2B1 is the likely hepatic uptake transporter of aliskiren (Vaidyanathan et al., *J Clin Pharmacol* 2008 48: 1323). Therefore, it is likely that the decrease by ciclosporin of aliskiren clearance is mediated inhibition of OATP2B1, ciclosporin being an inhibitor of OATP2B1 (Kalliokoski and Niemi M. Br J Pharmacol. 2009,158(3):693-705). The information reported in the current SmPC on the role of transporters (and their inhibitors) on aliskiren PK also need to be updated based on all available non clinical and clinical data. In particular, section 4.4, 4.5, 5.2 should be revised. The results of the published study on the effect of rifampicin on aliskiren PK (Tapaninen et al., Eur J Clin Pharmacol. 2010 May;66(5):497-502) should also be inserted in the revised SmPC.

1.3. Risk management plan

The Risk Management Plan (RMP), reflecting the removal of the contraindication of the concomitant administration of verapamil and aliskiren for Rasilez (RMP 7.0) and Rasilez HCT (RMP 7.0) were submitted during Rasilez II-41 and Rasilez II-05 procedures and were assessed in the frame of the relevant procedures.

2. Changes to the Product Information

The following changes to the current aliskiren product infomation are proposed by the MAH (underlined new text, strikethrough deleted text):

4.3 Contraindications

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The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent P-gp inhibitors, and other potent P-gp inhibitors (e.g. quinidine, ~~verapamil~~), is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

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Moderate P-gp inhibitors

Co-administration of aliskiren 300 mg with ketoconazole 200 mg or verapamil 240 mg resulted in a 76% or 97% increase in aliskiren AUC, respectively ~~but P-gp inhibitors such as ketoconazole are expected to increase tissue concentrations more than plasma concentrations~~. Therefore caution should be exercised when aliskiren is administered with moderate P-gp inhibitors such as ketoconazole or verapamil (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Digoxin and verapamil bioavailability may be slightly decreased by Rasilez.

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P-glycoprotein interactions

MDR1/Mdr1a/1b (P-gp) was found to be the major efflux system involved in intestinal absorption and biliary excretion of aliskiren in preclinical studies. Rifampicin, which is an inducer of P-gp, reduced aliskiren bioavailability by approximately 50% in a clinical study. Other inducers of P-gp (St. John's wort, ~~rifampicin~~) might ~~therefore~~ decrease the bioavailability of Rasilez. Although this has not been investigated for aliskiren, it is known that P-gp also controls tissue uptake of a variety of substrates and P-gp inhibitors can increase the tissue-to-plasma concentration ratios. Therefore, P-gp inhibitors may increase tissue levels more than plasma levels. The potential for drug interactions at the P-gp site will likely depend on the degree of inhibition of this transporter.

P-gp potent inhibitors

A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases C_{max} of aliskiren 75 mg approximately 2.5-fold and AUC approximately 5-fold. The increase may be higher with higher aliskiren doses. In healthy subjects, itraconazole (100 mg) increases AUC and C_{max} of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

Moderate P-gp inhibitors

Co-administration of ketoconazole (200 mg) or verapamil (240 mg) with aliskiren (300 mg) resulted in a 76% or 97% increase in aliskiren AUC, respectively. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

P-gp substrates or weak inhibitors

No relevant interactions with atenolol, digoxin, amlodipine or cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C_{max} increased by

50%.

~~Moderate P-gp inhibitors~~
~~Co-administration of ketoconazole (200 mg) with aliskiren (300 mg) resulted in an 80% increase in plasma levels of aliskiren (AUC and C_{max}). Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. The change in plasma levels of aliskiren in the presence of ketoconazole is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. Yet, P-gp inhibitors are expected to increase tissue concentrations more than plasma concentrations. Therefore, caution should be exercised when aliskiren is administered with ketoconazole or other moderate pgp inhibitors (itraconazol, clarithromycin, telithromycin, erythromycin, amiodarone).~~

~~P-gp potent inhibitors~~
~~A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases C_{max} of aliskiren 75 mg approximately 2.5 fold and AUC approximately 5 fold. The increase may be higher with higher aliskiren doses. In healthy subjects, itraconazole (100 mg) increases AUC and C_{max} of aliskiren (150 mg) by 6.5 fold and 5.8 fold, respectively. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).~~

Organic anion transporting polypeptide (OATP) inhibitors
Preclinical studies indicate that aliskiren might be a substrate of organic anion transporting polypeptides. Therefore, the potential exists for interactions between OATP inhibitors and aliskiren when administered concomitantly (see interaction with Grapefruit juice).

3. Conclusion

On 22 September 2011 the CHMP considered these Type II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.