23 September 2010
EMA/CHMP/479605/2012
Human Medicines Development and Evaluation

Assessment report

Rasilez, Riprazo, Sprimeo (aliskiren),

Rasilez HCT (aliskiren hemifumarate / hydrochlorothiazide)

Procedure No.: EMEA/H/C/xxxx/WS/0037

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 at once daily doses of 150 and 300 mg was approved in the EU on 21 June 2007, for use as monotherapy, or in combination with other anti-hypertensive agents, for the treatment of mild to moderate hypertension.

On 20 November 2008, the new fixed combination aliskiren/hydrochlorothiazide (Rasilez HCT), was approved 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.

Based on preclinical data, it is known that P-gp is a major determinant of aliskiren bioavailability. A clinical study conducted independently by Tapaninen et al. explored the pharmacokinetic interaction between aliskiren and itraconazole (a P-gp inhibitor) in healthy volunteers. The results of this study show that the exposure of aliskiren is increased by itraconazole when both drugs are administered concomitantly.

This application concerns the following medicinal products:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Rasilez	aliskiren	See Annex A
Rasilez HCT	aliskiren hemifumarate / hydrochlorothiazide	See Annex A
Riprazo	aliskiren	See Annex A
Sprimeo	aliskiren	See Annex A

The variation requested is the following:

Variations 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 concerns 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. 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.

1.2. Clinical aspects

Interaction study in healthy volunteers

Tapinen and co-workers performed a DDI study to investigate the effects of itraconazole on the pharmacokinetics (PK) and pharmacodynamics (PD) of aliskiren. In a randomized crossover study with 2 phases and a washout period of 4 weeks, healthy volunteers took either 100 mg itraconazole (first dose 200 mg) or placebo orally twice daily for 5 days. On Day 3, following an overnight fast, they received their morning dose of itraconazole or placebo. One hour later, a single oral dose of 150 mg aliskiren was administered with 150 mL of water. Blood samples were blood samples for drug concentration measurements were drawn prior to and 0.5, 1, 2, 3, 4, 5, 7, 9, 12, 24, 34, 48, and 72 hours after the administration of aliskiren. On Day 3, blood samples were also drawn (T = 0, 4 and 24 hr post dose) for the determination of plasma renin activity. On Day 3, urine was collected up to 12 hours to measure aliskiren. Systolic and diastolic blood pressures and heart rate were measured prior to and 2, 4, 7, 9, 12, and 24 hours after the administration of aliskiren.

Time-courses of aliskiren plasma levels with or without itraconazole are shown in the following figure:

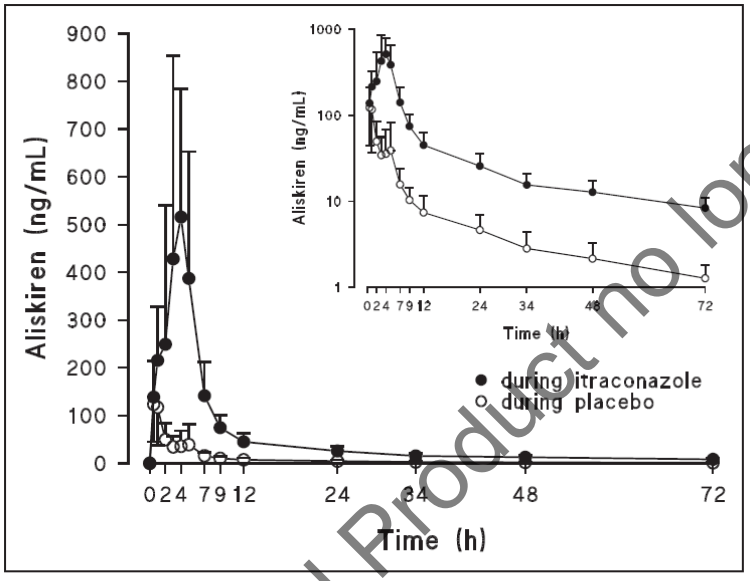

Figure 1. Mean ± SD plasma concentrations of aliskiren in 11 healthy volunteers after a single 150-mg oral dose of aliskiren on day 3 of a 5-day treatment with 100 mg itraconazole (first dose 200 mg) or placebo twice daily. Inset depicts the same data on a semi-logarithmic scale.

Aliskiren PK parameters with or without (placebo) itraconazole are shown in the following table:

Variable	Placebo Phase (Control)	Itraconazole Phase	Geometric Mean Ratio/ Mean Difference[a] (95% CI)	*P* Value
C_{max}, ng/mL	142 ± 82	766 ± 377	5.81 (3.09, 10.92)	<.001
t_{max}, h	1 (0.5-5)	4 (2-7)		.006
$t_{1/2}$, h	34.0 ± 9.7	36.2 ± 8.2	2.0 (-7.4, 11.4)	.643
$AUC_{0\text{-}72\,h}$, ng·h/mL	565 ± 275	3518 ± 1353	6.45 (4.19, 9.92)	<.001
$AUC_{0\text{-}\infty}$, ng·h/mL	625 ± 293	3957 ± 1458	6.54 (4.36, 9.81)	<.001
Ae, mg	0.567 ± 0.289	4.463 ± 2.079	8.00 (5.47, 11.69)	<.001
CL_{renal}, L/h	1.48 ± 0.24	1.80 ± 0.36	1.21 (1.01, 1.44)	.042

Data are given as mean ± SD, t_{max} data as median (range). CI, confidence interval; C_{max}, peak plasma concentration; t_{max}, time to C_{max}; $t_{1/2}$, elimination half-life; $AUC_{0\text{-}72\,h}$, area under the plasma concentration-time curve from 0 to 72 hours; $AUC_{0\text{-}\infty}$, area under the plasma concentration-time curve from time 0 to infinity; Ae, amount excreted into urine within 12 hours; CL_{renal}, renal clearance.
a. These data are geometric mean ratios (95% CI) for the C_{max}, AUC, Ae, and CL_{renal} values and mean difference (95% CI) for the $t_{1/2}$.

Itraconazole markedly increased aliskiren AUC and Cmax but did not change t1/2 or CL.

The Cmax and AUC0-13 h of itraconazole and hydroxyitraconazole showed no significant correlation with the relative increase in the Cmax or AUC0-∞ of aliskiren.

Plasma renin activity 24 hours after aliskiren intake was 68% lower during the itraconazole phase than during the placebo phase. No significant difference existed in the systolic or diastolic blood pressure or the heart rate between the itraconazole and placebo phases.

The authors concluded that this interaction is probably mediated by inhibition of the P-gp-mediated efflux of aliskiren in the small intestine, with a possible, minor contribution from inhibition of CYP3A4.

Considering that the reported change in aliskiren AUC induced by itraconazole in the presence of 150 mg aliskiren is higher than that with cyclosporine, the MAH's conclusion is that it is appropriate to consider itraconazole as a potent P-gp inhibitor and to advise against concomitant use in a similar manner to cyclosporine.

Changes to the Product Information

The following changes to the current aliskiren and aliskiren/Hctz product information are proposed by the MAH:

RASILEZ / SPRIMEO / RIPRAZO	
Note for the reviewer: **- Additions related to the contraindication with itraconazole are in blue** **- Additions related to new QRD template are in green** **- Deletions are in ~~red strikethrough~~**	
SUMMARY OF PRODUCT CHARACTERISTICS	
PRESENT [10,11]	**PROPOSED** [10, 11]
4.3 Contraindications The concomitant use of aliskiren with ciclosporin, ~~a~~ highly potent P-gp inhibitor, and other potent P-gp inhibitors (quinidine, verapamil), is contraindicated (see section 4.5).	**4.3 Contraindications** The concomitant use of aliskiren with ciclosporin **and itraconazole**, **two** highly potent P-gp inhibitor**s**, and other potent P-gp inhibitors (quinidine, verapamil), is contraindicated (see section 4.5).
4.5 Interaction with other medicinal products and other forms of interaction 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. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).	**4.5 Interaction with other medicinal products and other forms of interaction** 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).
4.6 Pregnancy and lactation ~~**Lactation**~~ It is not known whether aliskiren is excreted in human milk. [Rasilez/Sprimeo/Riprazo] was secreted in the milk of lactating rats. Its use is therefore not recommended in women who are breast-feeding	**4.6 Fertility, pregnancy and lactation** **Breast-feeding** It is not known whether aliskiren is excreted in human milk. [Rasilez/Sprimeo/Riprazo] was secreted in the milk of lactating rats. Its use is therefore not recommended in women who are breast-feeding.

4.8 Undesirable effects The adverse drug reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), ~~including isolated reports.~~ Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness Angioedema has occurred during treatment with [Rasilez/Sprimeo/Riprazo]. In controlled clinical trials, angioedema occurred rarely during treatment with [Rasilez/Sprimeo/Riprazo] with rates comparable to treatment with placebo or hydrochlorothiazide. Cases of angioedema have also been reported in post-marketing experience (frequency ~~unknown~~). In the event of any signs suggesting an allergic reaction (in particular difficulties in breathing, or swallowing, or swelling of the face, extremities, eyes, lips and/or tongue) patients should discontinue treatment and contact the physician (see section 4.4).	**4.8 Undesirable effects** The adverse drug reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000) **and not known (cannot be estimated from the available data).** Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Angioedema has occurred during treatment with [Rasilez/Sprimeo/Riprazo]. In controlled clinical trials, angioedema occurred rarely during treatment with [Rasilez/Sprimeo/Riprazo] with rates comparable to treatment with placebo or hydrochlorothiazide. Cases of angioedema have also been reported in post-marketing experience (frequency **not known).** In the event of any signs suggesting an allergic reaction (in particular difficulties in breathing, or swallowing, or swelling of the face, extremities, eyes, lips and/or tongue) patients should discontinue treatment and contact the physician (see section 4.4).
10. DATE OF REVISION OF THE TEXT	**10. DATE OF REVISION OF THE TEXT** **Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu**
CONDITIONS OF THE MARKETING AUTHORISATION	
• **OTHER CONDITIONS** Risk Management Plan As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, updated RMP should be submitted at the same time as the ~~next~~ Periodic Safety Update Report (PSUR). In addition, an updated RMP should be submitted: • When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities. • Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached. • At the request of the **EMEA.**	• **OTHER CONDITIONS** Risk Management Plan As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, **any** updated RMP should be submitted at the same time as the **following** Periodic Safety Update Report (PSUR). In addition, an updated RMP should be submitted: • When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities. • Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached. • At the request of the **European Medicines Agency.**
PACKAGE LEAFLET	
PRESENT [10,11]	**PROPOSED** [10, 11]
2. BEFORE YOU TAKE RASILEZ/SPRIMEO/RIPRAZO **Do not take [Rasilez/Sprimeo/Riprazo]** - if you are taking ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g. rheumathoid arthritis or atopic dermatitis) ~~or~~ verapamil (a medicine used to lower blood pressure, to correct hearth rhythm or to treat angina pectoris) or quinidine (a medicine used to correct heart rhythm).	**2. BEFORE YOU TAKE RASILEZ/SPRIMEO/RIPRAZO** **Do not take [Rasilez/Sprimeo/Riprazo]** - if you are taking ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g. rheumathoid arthritis or atopic dermatitis), **itraconazole** (a medicine used to treat fungal infections), verapamil (a medicine used to lower blood pressure, to correct hearth rhythm or to treat angina pectoris) or quinidine (a medicine used to correct heart rhythm).

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RASILEZ HCT

SUMMARY OF PRODUCT CHARACTERISTICS

PRESENT [10,11]	PROPOSED [10, 11]
4.3 Contraindications – The concomitant use of aliskiren with ciclosporin, a highly potent P-glycoprotein (P-gp) inhibitors, and other potent P-gp inhibitors (quinidine, verapamil), is contraindicated (see section 4.5).	**4.3 Contraindications** – The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent P-glycoprotein (P-gp) inhibitors, and other potent P-gp inhibitors (quinidine, verapamil), is contraindicated (see section 4.5).
4.5 Interaction with other medicinal products and other forms of interaction *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. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).	**4.5 Interaction with other medicinal products and other forms of interaction** *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).
4.6 Pregnancy and lactation ~~Lactation~~ Rasilez HCT is contraindicated during lactation (see section 4.3). It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. Thiazides appear in human milk and may inhibit lactation. They can produce adverse biological effects including hypokalaemia, haemolysis (glucose-6-phosphate dehydrogenase (G6PD) defect) and hypersensitivity due to sulphonamide properties.	**4.6 Fertility, pregnancy and lactation** Breast-feeding Rasilez HCT is contraindicated during lactation (see section 4.3). It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. Thiazides appear in human milk and may inhibit lactation. They can produce adverse biological effects including hypokalaemia, haemolysis (glucose-6-phosphate dehydrogenase (G6PD) defect) and hypersensitivity due to sulphonamide properties.
4.8 Undesirable effects The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. In controlled clinical trials, angioedema occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or hydrochlorothiazide. Cases of angioedema have also been reported in post-marketing experience (frequency unknown). In the event of any signs suggesting an allergic reaction patients should discontinue treatment and contact the physician (see section 4.4).	**4.8 Undesirable effects** The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. In controlled clinical trials, angioedema occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or hydrochlorothiazide. Cases of angioedema have also been reported in post-marketing experience (frequency not known). In the event of any signs suggesting an allergic reaction patients should discontinue treatment and contact the physician (see section 4.4).
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PACKAGE LEAFLET	
PRESENT [10,11]	**PROPOSED** [10, 11]
2. BEFORE YOU TAKE RASILEZ HCT - if you are taking ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g. rheumatoid arthritis or atopic dermatitis) ~~or~~ verapamil (a medicine used to lower blood pressure, to correct hearth rhythm or to treat angina pectoris) or quinidine (a medicine used to correct heart rhythm).	**2. BEFORE YOU TAKE RASILEZ HCT** - if you are taking ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g. rheumatoid arthritis or atopic dermatitis), itraconazole (a medicine used to treat fungal infections), verapamil (a medicine used to lower blood pressure, to correct hearth rhythm or to treat angina pectoris) or quinidine (a medicine used to correct heart rhythm).
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Overall discussion and benefit/risk assessment

The data from the study in healthy volunteers by *Tapinen et al.* further demonstrate that P-gp status has a very marked influence on the pharmacokinetics of aliskiren, thus justifying the precautionary approach to contraindicate concomitant use of aliskiren and potent P-gp inhibitors.

The addition of a contraindication for the concomitant use of itraconazole is endorsed by the CHMP and the proposed changes to section 4.3 and 4.5 of the SPC can be agreed.

The proposed changes to the annexes related to the implementation of the latest QRD template (version 7.3.1) are acceptable and the benefit/risk balance remains unchanged.

2. Conclusion

On 23 September 2010 the CHMP considered this Type II variation 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, Annex II and Package Leaflet (Attachment 1 - changes highlighted).

Variations(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 concerns 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. In addition, the MAH took the opportunity to update the annexes in line with the latest QRD template (version 7.3).