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TRANSPARENCY COMMITTEE
Opinion
4 December 2013

RASILEZ HCT 150 mg/12.5 mg, film-coated tablets

B/30 (CIP code: 34009 392 151 6 7)

RASILEZ HCT 150 mg/25 mg, film-coated tablets

B/30 (CIP code: 34009 392 152 2 8)

RASILEZ HCT 300 mg/12.5 mg, film-coated tablets

B/30 (CIP code: 34009 392 153 9 6)

RASILEZ HCT 300 mg/25 mg, film-coated tablets

B/30 (CIP code: 34009 392 154 5 7)

Applicant: NOVARTIS PHARMA S.A.S.

INN	Aliskiren / hydrochlorothiazide
ATC code (2008)	C09XA52 (aliskiren and hydrochlorothiazide)
Reason for the review	Re-assessment of the actual benefit and the improvement in actual benefit, on the initiative of the Transparency Committee (in pursuance of Article R-163-21 of the Social Security Code). Renewal of inclusion
Lists concerned	National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123-2)
Indications concerned	“Treatment of essential hypertension in adults. RASILEZ HCT is indicated in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone. RASILEZ HCT is indicated as substitution therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination.”

<p>AB</p>	<p>The Committee considers that the AB of RASILEZ HCT is:</p> <ul style="list-style-type: none"> - insufficient in hypertensive patients treated with a combination already containing an inhibitor of the renin-angiotensin-aldosterone system (CEI or ARB), including patients with diabetes or renal impairment, - insufficient in patients whose blood pressure is not adequately controlled on treatment containing hydrochlorothiazide used alone, - moderate in patients whose blood pressure is not adequately controlled by aliskiren used alone or in substitution therapy in patients whose blood pressure is adequately controlled by aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in RASILEZ HCT.
<p>Therapeutic use</p>	<p>Given the proven efficacy of aliskiren combined with hydrochlorothiazide only on blood pressure and the results observed in the ALTITUDE and ASTRONAUT studies of morbidity and mortality which demonstrated an absence of benefit in terms of cardiovascular prevention associated with an increased risk of adverse events (hyperkalaemia, renal impairment and hypotension) of aliskiren by comparison with placebo, in patients treated jointly with another inhibitor of the renin-angiotensin system, this combination (RASILEZ HCT) can be used only after the failure of the five other classes of antihypertensives which have demonstrated their efficacy and morbidity and mortality (diuretics, CEI, ARB, calcium channel blockers and beta blockers), used alone or in combination, and who are not being treated with another RAAS inhibitor (ARB or CEI).</p> <p>In addition, this combination is reserved for patients whose blood pressure is not adequately controlled by treatment containing aliskiren. In patients who are not controlled by a diuretic treatment, other classes of antihypertensives must be used first; there is thus no place for this combination. This fixed combination can also be used in substitution therapy in patients whose blood pressure is controlled by aliskiren and hydrochlorothiazide, given concurrently at the same dose.</p>
<p>Recommendations</p>	<p>The Committee wishes to re-assess this dossier in one year on the basis of the collected safety data.</p>

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised)	Date initiated: 16/01/2009 2013 revisions: addition of wordings and contraindications relating to dual blockade and to patients with renal failure in particular. The Marketing Authorisation for RASILEZ HCT is combined with an RMP which has been updated since the Committee's previous opinion to take account, in particular, of the results of the ALTITUDE study (see section 9.2.2).
Prescribing and dispensing conditions / special status	List I
ATC Classification (2013)	C :Cardiovascular system C09 :Agents acting on the renin-angiotensin system C09X :Other agents acting on the renin-angiotensin system C09XA :Renin-inhibitors C09XA52 :aliskiren and hydrochlorothiazide

02 BACKGROUND

Having regard to the Opinion given by the Transparency Committee on RASILEZ dated 6 February 2013 which took account of the clinical data from the ALTITUDE study and in pursuance of Article R.163-21 of the Social Security Code, the Transparency Committee wished to re-assess the actual benefit of the proprietary medicinal product RASILEZ HCT (fixed combination of aliskiren and hydrochlorothiazide).

The renewal of inclusion of these proprietary medicinal products on the list of medicines refundable by National Health Insurance for a period of 5 years starting from 25/08/2009 (Official Gazette of 25/08/2009) is also renewed in this Opinion.

03 THERAPEUTIC INDICATIONS

"Treatment of essential hypertension in adults.

RASILEZ HCT is indicated in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone.

RASILEZ HCT is indicated as substitution therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination."

04 DOSAGE

"The recommended dose of RASILEZ HCT is one tablet per day.

The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks.

Dosage in patients whose blood pressure is not adequately controlled with aliskiren or hydrochlorothiazide used alone: Individual dose titration with each of the two components may be recommended before changing to the fixed combination. When clinically appropriate, a direct change from monotherapy to the fixed combination may be considered. RASILEZ HCT 150 mg /12.5 mg may be administered in patients whose blood pressure is not adequately controlled with aliskiren 150 mg or hydrochlorothiazide 12.5 mg alone. If blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to a maximum of RASILEZ HCT

300 mg/25 mg daily. The dosage should be individualised and adjusted according to the patient's clinical response.

Dosage as substitution therapy: For convenience, patients receiving aliskiren and hydrochlorothiazide from separate tablets may be switched to a fixed combination tablet of RASILEZ HCT containing the same component doses.

Special populations

Renal impairment: No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see sections 4.4 and 5.2). Due to the hydrochlorothiazide component, RASILEZ HCT is contraindicated for use in patients with anuria and in patients with severe renal impairment (glomerular filtration rate (GFR) < 30 ml/min/1.73 m²).

The concomitant use of RASILEZ HCT with angiotensin II receptor blockers (ARB) or angiotensin converting enzyme inhibitors (CEI) is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.3, 4.4 and 5.2 of the SPC).

Hepatic impairment: RASILEZ HCT is contraindicated in patients with severe hepatic impairment and must be used with caution in patients with mild to moderate hepatic impairment or progressive liver disease. No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment (see sections 4.3, 4.4 and 5.2 of the SPC).

Patients aged 65 years and over: The recommended starting dose of aliskiren in elderly patients is 150 mg. No clinically meaningful additional blood pressure reduction is observed by increasing the dose to 300 mg in the majority of elderly patients.

Paediatric population: The safety and efficacy of RASILEZ HCT in children and adolescents aged below 18 years have not yet been established. No data are available."

05 THERAPEUTIC NEED^{1,2,3}

In uncomplicated essential hypertension, some thiazide diuretics, beta blockers, calcium-channel blockers, converting enzyme inhibitors and angiotensin II receptor blockers showed a benefit in the prevention of cardiovascular events and death from any cause in clinical trials.

The medicines in these classes are therefore recommended for first-line use in the management of patients with uncomplicated essential hypertension.

In most hypertensive patients, therapeutic needs are met by using these five classes of antihypertensives.

In patients who are not controlled by medicines in these five classes, used alone or in combination, other classes of antihypertensives that have shown their efficacy only in the reduction of blood pressure can be used: vasodilators, alpha blockers, centrally-acting antihypertensives.

¹ SFHTA (Société Française d'HyperTension Artérielle). Blacher J et al. Prise en charge de l'hypertension artérielle de l'adulte. Press Med. 2013; 42: 819-25.

² ESH (European Society of Hypertension) & ESC (European Society of Cardiology). Mancia G, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013; 34: 2159-219.

³ NICE (National Institute for Health and Care Excellence). Hypertension. Clinical management of primary hypertension in adults. NICE Clinical Guideline 34. August 2011.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Aliskiren (RASILEZ) is the only representative of the class of renin inhibitors currently available. The comparators of RASILEZ HCT (aliskiren + HCTZ) are antihypertensive medicines that have demonstrated their efficacy only in terms of the reduction in blood pressure, used in combination with hydrochlorothiazide (ESIDREX in the case of a free combination).

NAME (INN) Company	Same TC* Yes/No	Indication	Date of opinion	AB/IAB (Wording)	Reimbursement Yes/No
Alpha blockers**					
ALPRESS (prazosin) Pfizer	No	Hypertension	18/07/2012	Substantial AB after considering all the therapeutic alternatives that have shown their efficacy on cardiovascular morbidity and mortality	Yes
MINIPRESS (prazosin) Cutis	No	Hypertension	20/06/2011	Insufficient AB	No
EUPRESSYL MEDIATENSYL (urapidil) Takeda	No	Hypertension	05/09/2012	Substantial AB starting from the triple therapy stage	Yes
Centrally acting antihypertensives**					
ALDOMET (methyldopa) Iroko Products Ld	No	Moderate to severe hypertension	06/03/2012	Substantial AB starting from the triple therapy stage	Yes
CATAPRESSAN (clonidine) Boehringer Ingelheim	No	Hypertension	04/09/2012	Substantial AB starting from the triple therapy stage	Yes
HYPERIUM (rilmenidine) Servier	No	Hypertension	09/03/2011	Moderate AB	Yes
PHYSIOTENS (moxonidine) Abbott	No	Hypertension	09/03/2011	Moderate AB	Yes
Centrally-acting antihypertensives in fixed combination					
TENSIONORME (bendroflumethiazide, reserpine) Lisa-Pharm	No	Hypertension	20/02/2008	Substantial AB starting from the triple therapy stage	Yes

*therapeutic category ** for combination with hydrochlorothiazide (ESIDREX) in free combination.

► Conclusion

The comparators listed are all clinically relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If not, why not	Population(s) That of the Marketing Authorisation or restricted
Germany	Yes	
Austria	Yes	
Belgium	Yes	
Spain	Yes	
Finland	No (not on the market)	-
Greece	Yes	
Ireland	Yes	-
Italy	Yes	-
Luxembourg	Yes	
Norway	No (not on the market)	-
Netherlands	Yes	
Portugal	Yes	
United Kingdom	No (not on the market)	-
Switzerland	Yes	

08 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion (reason for request)	27/05/2009 Inclusion
Indication	“Treatment of essential hypertension in adults. RASILEZ HCT is indicated in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone. RASILEZ HCT is indicated as substitution therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination.”
AB	Substantial
IAB	IAB V by comparison with concurrent use of each of the components taken separately

09 ANALYSIS OF AVAILABLE DATA

The company supplied studies which evaluated the efficacy of RASILEZ HCT in terms of the reduction in blood pressure:

- two studies (Basile 2011,⁴ Black 2010⁵) which compared, respectively, the efficacy of hydrochlorothiazide (HCT) and of aliskiren as monotherapy with the aliskiren/HCT combination, performed in hypertensive patients followed up for 4 to 12 weeks.
- two studies (Townsend 2011⁶ and Ferdinand 2011⁷), which compared the efficacy of aliskiren + HCT with amlodipine alone in hypertensive patients followed up for 8 weeks.
- a study (Whaley-Connell 2011⁸) which compared the efficacy of aliskiren + HCT with ramipril alone, performed in hypertensive patients followed up for 8 weeks.
- two studies (Geiger 2009⁹ and Lacourcière 2012¹⁰) which compared the efficacy of triple therapy containing aliskiren with dual therapies containing each of the components of the triple therapy performed in hypertensive patients followed up for 8 weeks.

A summary of the results of the ALTITUDE study,¹¹ given in the Opinion of 6 February 2013 for RASILEZ (aliskiren) in hypertensive patients and of the ASTRONAUT study,¹² performed in heart-failure patients (off-label), will also be presented below.

09.1 Efficacy

9.1.1. Studies of the reduction in blood pressure

Study versus aliskiren alone

The Black 2010⁵ study confirms the significantly greater efficacy of the aliskiren + HCT combination versus aliskiren alone in terms of the reduction in blood pressure.

Study versus HCT alone

The Basile 2011⁴ study confirms the significantly greater efficacy of the aliskiren + HCT combination versus HCT alone in terms of the reduction in blood pressure.

Studies versus amlodipine alone

The Townsend 2011⁶ and Ferdinand 2011⁷ studies evaluated the efficacy of the aliskiren + HCT combination versus amlodipine alone in terms of the reduction in systolic blood pressure (SBP) in 860 diabetic patients (Townsend study) or 332 Afro-American patients (Ferdinand study); the treatments were administered by forced titration.

After 8 weeks of treatment:

⁴ Basile et al. Comparison of Aliskiren/Hydrochlorothiazide Combination Therapy With Hydrochlorothiazide monotherapy in Older Patients With Stage 2 Systolic Hypertension: Results of the ACTION Study. *J Clin Hypertens*. March 2011.

⁵ Black et al. Aliskiren Alone or in Combination With Hydrochlorothiazide in Patients With the Lower Ranges of Stage 2 Hypertension: The ACQUIRE Randomized Double-Blind Study. *The Journal of Clinical Hypertension*. December 2010.

⁶ Townsend et al. Comparison of Aliskiren/Hydrochlorothiazide Combination Therapy and Amlodipine Monotherapy in Patients With Stage 2 Systolic Hypertension and Type 2 Diabetes Mellitus. *J Clin Hypertens*. 2011; 13: 889–897.

⁷ Ferdinand et al. Peripheral and Central Blood Pressure Responses of Combination Aliskiren/Hydrochlorothiazide and Amlodipine Monotherapy in African American Patients With Stage 2 Hypertension: The ATLAAS Trial. *Clin Hypertens*. 2011; 13: 366–375.

⁸ Whaley-Connell et al. Central Pressure and Biomarker Responses to Renin Inhibition with Hydrochlorothiazide and Ramipril in Obese Hypertensives: The ATAIN Study. *Cardiorenal Med* 2011; 1: 53–66.

⁹ Geiger et al. Combination Therapy With Various Combinations of Aliskiren, Valsartan, and Hydrochlorothiazide in Hypertensive Patients Not Adequately Responsive to Hydrochlorothiazide Alone. *J Clin Hypertens* 2009; 11: 324–332.

¹⁰ Lacourcière et al. Clinic and ambulatory blood pressure lowering effect of aliskiren/amlodipine/hydrochlorothiazide combination in patients with moderate-to-severe hypertension: a randomized active-controlled trial. *J Hypertens* 2012, 30: 2047–2055.

¹¹ Parving HH et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *NEJM online*, November 3, 2012.

¹² Gheorghide et al. Effect of Aliskiren on Postdischarge Mortality and Heart Failure Readmissions Among Patients Hospitalized for Heart Failure The ASTRONAUT Randomized Trial. *JAMA*, March 20, 2013.

- in the Townsend study, a significantly greater reduction in SBP was observed in the aliskiren + HCT group versus the amlodipine group: -28.8 mmHg versus -26.2 mmHg, $p < 0.05$,
- in the Ferdinand study, no significant difference was observed between the two treatment groups.

Studies versus ramipril alone:

The Whaley-Connell 2011⁸ study evaluated the efficacy of the aliskiren + HCT combination versus ramipril alone in terms of the reduction in systolic blood pressure (SBP) in 386 obese patients; the treatments were administered by forced titration.

After 8 weeks of treatment, a significantly greater reduction in SBP was observed in the aliskiren + HCT group versus the ramipril group: -27.9 mmHg versus -16.4 mmHg, difference -11.5 mmHg [-14.6; -8.4], $p < 0.0001$.

Studies comparing dual or triple therapies:

The Geiger 2009⁹ study compared various combinations: aliskiren + valsartan + HCT, aliskiren + HCT, valsartan + HCT and HCT 25 mg alone. The efficacy of these treatments was evaluated in terms of the reduction in diastolic blood pressure (DBP) in 641 patients who were uncontrolled after 4 weeks of treatment with HCT 25 mg ($95 \text{ mmHg} < \text{DBP} < 110 \text{ mmHg}$).

After 8 weeks of treatment, the results of this study confirm the significantly greater efficacy of a triple therapy (aliskiren + valsartan + HCT) compared with a dual therapy (valsartan + HCT or aliskiren + HCT) in patients not controlled by monotherapy with HCT 25 mg in terms of the reduction in DBP.

Similarly, the study by Lacourcière¹⁰ compared various combinations: aliskiren + amlodipine + HCT, aliskiren + HCT, amlodipine + HCT and aliskiren + amlodipine. The efficacy of these treatments was assessed in terms of the reduction in blood pressure (DBP and SBP) in 1191 patients with moderate to severe hypertension; the treatments were administered by forced titration.

After 8 weeks of treatment, the results of this study confirm the significantly greater efficacy of a triple therapy (aliskiren + amlodipine + HCT) by comparison with a dual therapy (aliskiren + HCT or aliskiren + amlodipine or amlodipine + HCT) in patients with moderate to severe hypertension.

In view of their duration (4 to 8 weeks), these studies, which evaluated the efficacy of aliskiren in combination with HCT and/or valsartan or with amlodipine, solely in terms of the reduction in blood pressure by comparison with other active comparators (amlodipine, ramipril, valsartan, used alone or in combination), cannot provide any reassuring data in patients who are uncontrolled despite use of the aforementioned five classes, used alone or in combination with each other, and who were not treated with another RAAS inhibitor (CEI or ARB).

9.1.2. Studies of morbidity and mortality

ALTITUDE study (see Committee Opinion of 6/02/2013 on RASILEZ)

"Aliskiren (RASILEZ) has been on the market since 2008 in the indication "treatment of essential hypertension".

Since it went on the market, a morbidity and mortality study (the ALTITUDE study) has provided new information:

The aim of this study was to compare aliskiren with placebo, both in combination with a conventional treatment containing a CEI or an ARB, in terms of morbidity and mortality in patients with type II diabetes and renal impairment. The primary efficacy endpoint was a combination of cardiovascular death, sudden death after resuscitation, MI or non-fatal stroke, hospitalisation due to heart failure, end-stage renal failure or renal-related death, and doubling of blood creatinine for at least one month.

This study was stopped at the second interim analysis, due to an increase in the aliskiren group:

- in the number of events making up the combined primary efficacy endpoint (cardiovascular death, sudden death after resuscitation, MI or non-fatal stroke, hospitalisation due to heart failure, end-stage renal failure or renal-related death, doubling of blood creatinine for at least one month): 748 patients (17.5%) in the aliskiren group versus 686 (16%) in the placebo group: HR 1.107 [0.996; 1.231], NS.
- an excess in the number of strokes (secondary endpoint) observed in the aliskiren group: 144 patients (13.4%) in the aliskiren group and 113 patients (12.6%) in the placebo group, HR 1.29 [1.01; 1.65], $p=0.043$,
- an excess of adverse effects observed in the aliskiren group: hyperkalaemia, hypotension and renal impairment.

In view of these results and following a re-assessment carried out by the EMA, contraindications, precautions for use, drug interactions and adverse effects were added to the Marketing Authorisation for RASILEZ.

After a median follow-up period of 32.9 months:

- The number of observed events making up the combined primary efficacy endpoint was: 783 (18.3%) in the aliskiren group and 732 (17.1%) in the placebo group: HR 1.08 [0.98; 1.20], NS.
- Strokes (secondary endpoint) were observed in 147 patients (3.4%) in the aliskiren group and 122 patients (2.8%) in the placebo group, HR 1.22 [0.96; 1.55], NS.
- Resuscitated cardiac arrests (secondary endpoint) were observed in 19 patients (0.4%) in the aliskiren group and 8 patients (0.2%) in the placebo group, HR 2.40 [1.05; 5.48], $p=0.04$.

These observations led the EMA to:

- contraindicate the combination of aliskiren with an ARB or a CEI in patients with diabetes or renal failure ($GFR < 60 \text{ ml/min/1.73 m}^2$) and not recommend this combination in other patients,
- add special precautions for use in instances where aliskiren is combined with an NSAID, due to the risk of hyperkalaemia and the negative impact on renal function."

ASTRONAUT study:

The aim of this randomised double-blind study was to compare the efficacy of aliskiren with a placebo, in combination with the standard treatments, in terms of cardiovascular death or re-hospitalisations on account of heart failure (combined primary efficacy endpoint), in 1615 haemodynamically stable patients hospitalised on account of heart failure.

After 12 months' follow-up, no significant reduction in cardiovascular deaths or re-hospitalisations on account of heart failure was shown between the groups: 283 events (35%) in the aliskiren group versus 301 (37.3%) in the placebo group, HR 0.93 [0.79; 1.09], NS.

The results of this study confirm those of the ALTITUDE study concerning the absence of benefit for aliskiren by comparison with placebo in terms of cardiovascular prevention associated with an increase in the risk of adverse events (hyperkalaemia, renal impairment, hypotension, see section 4.2) in patients most of whom were treated with another inhibitor of the renin-angiotensin system (85% of the patients in the study).

09.2 Adverse effects

9.2.1. Clinical study data

Studies on the reduction in blood pressure:

These studies did not reveal any new safety signal. In view of their limited follow-up period (4 to 12 weeks), these studies cannot be used to ascertain the long-term safety of the aliskiren + HCT combination in patients with hypertension.

ALTITUDE study (see Committee Opinion of 6/02/2013 on RASILEZ)

“In terms of adverse effects, the data from the ALTITUDE study also showed, particularly when aliskiren is combined with another inhibitor of the renin-angiotensin-aldosterone system (CEI or ARB) in diabetic patients with renal impairment:

- *A larger number of strokes and an increase in adverse events such as hypotension and hyperkalaemia.*
- *Impairment of renal function, including acute renal failure.”*

ASTRONAUT study

In this study, adverse effects were observed in 1337 patients (82.6%): 670 (82.9%) patients in the aliskiren group versus 667 (82.3%) in the placebo group. The most common significant adverse events were:

- hyperkalaemia: 20.9% versus 17.5%, HR 1.19 [0.98; 1.46], NS,
- impairment of renal function or renal failure: 16.6% versus 12.1%, HR 1.37 [1.08; 1.75], p=0.01,
- hypotension: 17.1% versus 12.6%, HR 1.36 [1.07; 1.72], p=0.01.

Discontinuations of treatment on account of adverse effects were significantly more common in the aliskiren group than in the placebo group: 11.8% versus 7.4%, p=0.003.

9.2.2. PSUR data

The analysis of the periodic safety update reports (PSUR) for RASILEZ HCT covering the period from 18 January 2008 to 18 January 2013 allows patients' exposure to treatment to be estimated at 600,656 patient-years. During this period, 3733 adverse effects were reported, 1535 of them serious.

As regards the serious adverse effects identified in the ALTITUDE and ASTRONAUT studies, their frequencies were as follows:

- stroke: 36 notified cases corresponding to a notification rate of 0.60 cases/1000 patient-years,
- renal impairment: 45 cases, 0.75 cases /1000 patient-years,
- hyperkalaemia: 25 cases, 0.42 cases /1000 patient-years,
- hypotension: 137 cases, 2.28 cases/1000 patient-years.

During this period, 42 deaths were observed, 1 of which was linked to treatment (by hyperkalaemia).

In the SPC, the safety profile of RASILEZ HCT was amended to take account of the results of the ALTITUDE study.

In addition, the analysis of the most recent PSUR revealed a new signal relating to hepatic events (elevations of liver enzymes).

The RMP for RASILEX HCT now includes follow-up of new identified risks:

- cardiovascular events,
- acute myocardial infarction,
- gastrointestinal haemorrhage,
- stroke.

Other previously identified events continue to be followed up, namely:

- diarrhoea,
- angioedema and anaphylactic reactions,
- hyperkalaemia,
- renal failure,
- hypotension including loss of consciousness/syncope.

The following potential risks also continue to be followed up:

- colorectal hyperplasia,
- ischaemic colitis,
- gastrointestinal haemorrhage,
- cancer,
- cardiac arrhythmia,
- elevation of liver enzymes.

09.3 Usage/prescription data

According to IMS-EPPM data (moving annual total, summer 2013), 175,653 prescriptions were issued for RASILEZ HCT, most of them (94%) for hypertension.

09.4 Summary & discussion

Main efficacy results:

In support of its application, the company provided seven studies which evaluated the efficacy of RASILEZ HCT in terms of the reduction in blood pressure (Basile 2011, Black 2010, Townsend 2011, Ferdinand 2011, Whaley-Connell 2011, Geiger 2009 and Lacourcière 2012). These studies confirm the superiority of the aliskiren + HCT combination over aliskiren alone and over HCT alone and the superiority of triple therapy with antihypertensives by comparison with dual therapy in terms of the reduction in blood pressure.

The company also reported two studies of morbidity and mortality: ALTITUDE and ASTRONAUT:

1. The ALTITUDE study which compared aliskiren with placebo, both in combination with a standard treatment comprising a CEI or an ARB in type II diabetics with renal impairment. The primary efficacy endpoint was a combination of cardiovascular death, sudden death after resuscitation, MI or non-fatal stroke, hospitalisation due to heart failure, end-stage renal failure or renal-related death, and doubling of blood creatinine lasting for at least one month.

This study was stopped at the second interim analysis, due to an excess, in the aliskiren group by comparison with the placebo group:

- of events comprising the primary efficacy endpoint: 748 patients (17.5%) versus 686 patients (16%): HR 1.107 [0.996; 1.231], NS.
- of stroke: 144 patients (13.4%) versus 113 patients (12.6%) in the placebo group, HR 1.29 [1.01; 1.65], p=0.043,
- of adverse effects: hyperkalaemia, hypotension and renal impairment.

In view of these results and following a re-assessment carried out by the EMA, contraindications, precautions for use, drug interactions and adverse effects were added to the Marketing Authorisation for RASILEZ.

After a median follow-up period of 32.9 months, there is an excess in the aliskiren group, by comparison with the placebo group:

- of events comprising the primary efficacy endpoint: 783 patients (18.3%) versus 732 patients (17.1%): HR 1.08 [0.98; 1.20], NS.
- of stroke: 147 patients (3.4%) versus 122 patients (2.8%), HR 1.22 [0.96; 1.55], NS.
- of resuscitated cardiac arrests: 19 patients (0.4%) versus 8 patients (0.2%), HR 2.40 [1.05; 5.48], p=0.04.

2. The ASTRONAUT study which compared aliskiren with placebo, both in combination with the standard treatments, in 1615 haemodynamically stable patients hospitalised on account of heart failure (off-label indication).

After a follow-up period of 12 months, the combined primary efficacy endpoint, including cardiovascular death or re-hospitalisation on account of heart failure, showed no difference between aliskiren and placebo: 283 (35%) versus 301 (37.3%), HR 0.93 [0.79; 1.09], NS.

Main safety results:

The studies with the aim of evaluating efficacy in reducing blood pressure did not reveal any new safety signal. Nevertheless, in view of their limited follow-up period (4 to 12 weeks), these studies cannot be used to prove the long-term safety of aliskiren in hypertensive patients.

The ALTITUDE study showed, particularly when aliskiren is combined with another inhibitor of the renin-angiotensin-aldosterone system (CEI or ARB), in diabetic patients with renal impairment:

- an increase in hypotension, hyperkalaemia,
- and impairment of renal function, including acute renal failure.

In the ASTRONAUT study, adverse effects were observed in 1337 patients (82.6%): 670 (82.9%) patients in the aliskiren group versus 667 (82.3%) in the placebo group. This study showed:

- hyperkalaemia: 20.9% versus 17.5%, HR 1.19 [0.98; 1.46], NS,
- impairment of renal function or renal failure: 16.6% versus 12.1%, HR 1.37 [1.08; 1.75], p=0.01,
- hypotension: 17.1% versus 12.6%, HR 1.36 [1.07; 1.72], p=0.01.
- discontinuation of treatment on account of AEs: 11.8% versus 7.4%, p=0.003.

Analysis of the most recent PSUR revealed a new signal relating to the elevation of liver enzymes.

Discussion:

The greater incidence of adverse events which was already known with aliskiren (hyperkalaemia, renal impairment, hypotension), and observed in the ALTITUDE study, was confirmed in the ASTRONAUT study. The results of this study confirm those of the ALTITUDE study concerning the absence of benefit for aliskiren by comparison with placebo in terms of cardiovascular prevention associated with an increase in the risk of adverse events (hyperkalaemia, renal impairment, hypotension) in patients most of whom were treated with another inhibitor of the renin-angiotensin system (85% of the patients in the study).

Also, in view of their duration (4 to 8 weeks), these studies, which evaluated the efficacy of aliskiren in combination with HCT and/or valsartan or amlodipine, in terms of the reduction in blood pressure by comparison with other active comparators (amlodipine, ramipril, valsartan, used alone or in combination), cannot provide any reassuring data in patients who are uncontrolled despite use of the aforementioned five classes, used alone or in combination with each other, and who were not treated with another RAAS inhibitor (CEI or ARB), taking account of the recommendations and contraindications of the Marketing Authorisation as specified in the Opinion of 6 February 2013 on RASILEZ (aliskiren).

Finally, the efficacy of the combination aliskiren + HCT (RASILEZ HCT) in terms of morbidity and mortality has not been demonstrated to date.

09.5 Planned studies

The company has not reported any studies, either in progress or to come.

010 THERAPEUTIC USE^{1,1,1}

Hygiene and dietary measures are recommended for all hypertensive patients regardless of their blood pressure, with or without associated drug treatment.

In uncomplicated essential hypertension, some thiazide diuretics, beta blockers, calcium-channel blockers, converting-enzyme inhibitors and angiotensin II receptor blockers showed a benefit in the prevention of cardiovascular events and death from any cause.

The medicines in these classes are therefore recommended for first-line use in the management of patients with uncomplicated essential hypertension.

In most hypertensive patients, therapeutic needs are met by using these five classes of antihypertensives.

In patients who are not controlled by medicines in these five classes, used alone or in combination, other classes of antihypertensives that have shown efficacy only in the reduction of blood pressure can be used: vasodilators, alpha blockers, centrally-acting antihypertensives.

Place of RASILEZ HCT:

In view of:

- the demonstrated efficacy of aliskiren, combined with hydrochlorothiazide only on blood pressure,
- the absence of benefit in terms of cardiovascular prevention combined with an increased risk of adverse events (hyperkalaemia, renal impairment, hypotension) of aliskiren by comparison with placebo, in patients treated jointly with another inhibitor of the rennin-angiotensin system, **the combination (RASILEZ HCT) can be used only after the failure of the five other classes of antihypertensives, used alone or in combination, and who are not being treated with another RAAS inhibitor (CEI or ARB).**

In the aforementioned setting, RASILEZ HCT can be used, as above, in substitution treatment in patients whose blood pressure is controlled by aliskiren and hydrochlorothiazide, administered jointly at the same dose and in patients whose blood pressure is not sufficiently controlled by aliskiren used alone.

In patients who are not controlled by a diuretic, other classes of antihypertensives must be used first; there is thus no place for RASILEZ HCT.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

▮ Essential arterial hypertension, due to its complications, can be life-threatening.

▮ This medicinal product is intended as a preventive therapy.

▮ In the majority of hypertensive patients, the therapeutic needs are covered by the use of the five classes of antihypertensives (diuretics, CEI, ARB, calcium-channel blockers and beta blockers), most of the active substances of which have demonstrated a benefit in morbidity and mortality, in the prevention of cardiovascular events and death from any cause.

In view of:

- the observation, in a study of morbidity and mortality (ALTITUDE), of an excess of cardiovascular events (stroke), and an increased incidence of adverse events which are

already known with aliskiren (hyperkalaemia, renal impairment, hypotension), by comparison with placebo, in patients already treated with another blocker of the rennin-angiotensin-aldosterone system (RAAS) (ARB or CEI),

- the confirmation of the absence of any benefit in terms of cardiovascular prevention in the ASTRONAUT study associated with an increase in adverse events (hyperkalaemia, renal impairment, hypotension) for aliskiren, by comparison with placebo, in patients treated mainly with another inhibitor of the renin-angiotensin system (85% of the patients in the study),

the efficacy/adverse effects ratio of RASILEZ HCT in patients with dual blockade of the RAAS is unfavourable.

In addition, in the absence of any available data, the use of aliskiren is not recommended in patients with severe renal failure (GFR < 30 ml/min/1.73 m²); its efficacy/adverse effects ratio in these patients therefore cannot be established.

For other patients, in view of:

- the antihypertensive effect of aliskiren combined with hydrochlorothiazide, demonstrated in periods of up to 8 weeks,
- the absence of available long-term data for aliskiren,
- the absence of any demonstrated efficacy for aliskiren in terms of morbidity and mortality,
- the safety profile of aliskiren,

the efficacy/adverse effects ratio for RASILEZ HCT is moderate.

► Aliskiren in fixed combination with hydrochlorothiazide is an antihypertensive which must be reserved for last-line use in patients who are not controlled by any of the five classes of antihypertensives (alone or in combination) that have demonstrated their efficacy in terms of morbidity and mortality and who have not been treated with any other inhibitor of the rennin-angiotensin system (CEI or ARB). In terms of therapeutic use, whereas hydrochlorothiazide can be added where blood pressure is not adequately controlled or control has failed in a patient who is already being treated with aliskiren, the reverse is not the case.

Public health benefit:

The public health burden of essential hypertension and cardiovascular diseases, which are a risk factor, is substantial.

The reduction in morbidity and mortality attributable to hypertension is a public health need (identified GTNDO* and public health law priority).

However, existing treatments (including free combinations of aliskiren and hydrochlorothiazide) already help to meet this need.

There is no evidence of a benefit of treatment with this fixed-dose combination by comparison with free combinations of these two active substances (even in terms of compliance).

Consequently, RASILEZ HCT is not expected to benefit public health in this indication.

* GTNDO: *Groupe Technique National de Définition des Objectifs* [National Technical Group for the Definition of Public-Health Objectives] (DGS [Directorate-General for Health]-2003)

Taking account of all these points, the Committee considers that the actual benefit of RASILEZ HCT, a fixed combination of aliskiren and hydrochlorothiazide, is:

- **insufficient in hypertensive patients treated with a combination already containing an inhibitor of the renin-angiotensin-aldosterone system (CEI or ARB), including in patients with diabetes or renal impairment,**
- **insufficient in patients whose blood pressure is not adequately controlled by treatment containing hydrochlorothiazide used alone.**

In these populations, the Committee does not recommend continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

In addition, the Committee considers that the actual benefit of RASILEZ HCT is moderate:

- **in patients whose blood pressure is inadequately controlled by aliskiren used alone,**

- in patients whose blood pressure is sufficiently well controlled by aliskiren and hydrochlorothiazide, administered concurrently at the same dose as in RASILEZ HCT.

In these populations, the Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

► **Proposed reimbursement rate: 30%**

011.2 Target population

The target population for RASILEZ consists of patients who are not controlled by any of the five classes of antihypertensives that have demonstrated their efficacy in terms of morbidity and mortality, who are not being treated with monotherapy or a combination already containing an inhibitor of the renin-angiotensin-aldosterone system (CEI or ARB) and not being treated with hydrochlorothiazide. It also includes patients whose blood pressure is controlled by the free combination of the components of RASILEZ HCT.

The prevalence of HTA in France is estimated to be between 12 and 14 million adult patients.^{13,14} For information, an unpublished study regarding the methods of managing HTA in general practice (THALES/CEMKA 2010) shows that:

- 77% of patients receive an antihypertensive drug treatment,
- nearly 60% of them are treated with a combination of at least two antihypertensives,
- a CEI or ARB is prescribed in 43% of cases and nearly 90% of prescriptions include a fixed dual therapy.

The proportion of patients concerned by this proprietary medicinal product is not precisely quantifiable on the basis of the data available.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

► **Packaging:** Appropriate for the prescription conditions according to the indication, dosage and treatment duration.

► **Committee's request:**

The Committee wishes to re-assess this dossier in one year on the basis of the collected safety data.

¹³ Wagner A. et al. High blood pressure prevalence and control in a middle-aged French population and their associated factors: the MONA LISA Study. *Journal of hypertension* 2011; 29: 43-50.

¹⁴ Niveau tensionnel moyen et prévalence de l'hypertension artérielle chez les adultes de 18 à 74 ans, ENNS 2006-2007. *Thematic BEH* 49-50. 16 December 2008: 478.