HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion

4 December 2013

RASILEZ 150 mg, film-coated tablets

B/30 (CIP: 34009 399 008 4 1)

RASILEZ 300 mg, film-coated tablets

B/30 (CIP: 34009 399 009 0 2)

Applicant: NOVARTIS PHARMA S.A.S.

INN	Aliskiren
ATC code (2013)	C09XA02 (renin inhibitor)
Reason for the review	**Renewal of inclusion**
List concerned	**National Health Insurance** (French Social Security Code L.162-17)
Indication concerned	**"Treatment of essential hypertension in adults"**

AB	**Taking account of these points, the Committee considers that the actual benefit of RASILEZ (aliskiren):** **- remains 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,** **- is moderate in other patients, i.e. patients who are not controlled by the five classes of antihypertensives that have proven their efficacy in terms of 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 (CEI or ARB).**
Therapeutic use	**Taking account of the proven efficacy of aliskiren only on blood pressure and the absence of benefit in terms of the 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 renin-angiotensin system (ALTITUDE and ASTRONAUT studies), aliskiren (RASILEZ) 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 (ARB or CEI).**
Recommendations	**The Committee wishes to re-assess this dossier in one year on the basis of the collected safety data.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date initiated (centralised procedure): 22 August 2007 Since the Committee's previous Opinion, RASILEZ (aliskiren) has had its risk management plan updated (see section 4.2.2)
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 C09XA02 : aliskiren

02 BACKGROUND

Examination of the propriety medicinal products included on the list of medicines refundable by National Health Insurance for a 5-year period starting on 21.07.2009, by Order of 13.07.2009.

03 CHARACTERISTICS OF THE MEDICINAL PRODUCT

03.1 Therapeutic indications

"Treatment of essential hypertension in adults."

03.2 Dosage

See SPC

04 ANALYSIS OF THE NEW DATA AVAILABLE

04.1 Efficacy

The company provided:
Two studies (Basile 2011,[1] Black 2010[2]) which compared, respectively, hydrochlorothiazide (HCT) and aliskiren as monotherapy with the aliskiren/HCT combination in terms of the reduction in blood pressure in hypertensive patients followed up for 4 to 12 weeks. They confirm the superiority of the aliskiren+HCT combination over aliskiren alone in terms of the reduction in blood pressure.

[1] 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. 2011; 13: 162-9.
[2] 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. J Clin Hypertens 2010; 12: 917-26.

Given their duration of 4 to 12 weeks, these studies provide no information about the effect on morbidity and mortality of aliskiren in patients who are not controlled by the five classes of antihypertensives that have shown their efficacy in terms of morbidity and mortality (diuretics, CEI, ARB, calcium-channel blockers and beta blockers), used alone or in combination with each other, and who are not being treated with another inhibitor of the renin-angiotensin-aldosterone system (CEI or ARB).

A study in patients with heart failure is therefore off-label (ASTRONAUT study[3]).
This randomised double-blind study compared aliskiren with placebo, both in combination with the standard treatments, in 1615 haemodynamically stable patients hospitalised on account of heart failure.
After 6 months, the combined primary efficacy endpoint, cardiovascular death or re-hospitalisation on account of heart failure, showed no difference between aliskiren and placebo: 24.9% versus 26.5%, HR 0.92 [0.76; 1.12], NS. These results were confirmed after 12 months' follow-up: 35% versus 37.3%; HR 0.93 [0.79; 1.09], NS.
This study confirms the results of the ALTITUDE study (see RASILEZ Opinion of 6 February 2013), i.e. 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).

04.2 Adverse effects

4.2.1. Data from clinical studies

ASTRONAUT study:
Adverse effects were observed in 82.9% of patients in the aliskiren group and 82.3% of those in the placebo group. The adverse events that were more common with aliskiren than with placebo 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 more common with aliskiren than with placebo: 11.8% versus 7.4%, p=0.003.

4.2.2. PSUR data

The analysis of the most recent periodic safety update report (PSUR) for RASILEZ (aliskiren) covering the period from 1 October 2011 to 30 September 2012 allows patients' exposure to treatment to be estimated at 718,311 patient-years. During this period, 4342 adverse effects were reported, of which 1860 showed one severity criterion.
The most commonly observed serious adverse effects were:
- increased creatinine,
- hyperkalaemia,
- hypotension,
- strokes.

In the light of the results of the ALTITUDE study, the safety profile of aliskiren was changed. **The RMP for aliskiren now includes follow-up of these new identified risks:**
- **cardiovascular events,**
- **acute myocardial infarction,**
- **gastrointestinal haemorrhage,**

[3] Gheorghiade et al. Effect of Aliskiren on Postdischarge Mortality and Heart Failure Readmissions Among Patients Hospitalized for Heart Failure The ASTRONAUT Randomized Trial. JAMA 2013; 309: 1125-35.

- **stroke**.

Other previously identified events continue to be followed up, namely:
- diarrhoea,
- angioedema and anaphylactic reactions,
- cancer,
- cardiac arrhythmia,
- colorectal hyperplasia,
- ischaemic colitis,
- hyperkalaemia,
- loss of consciousness, syncope,
- renal failure,
- elevation of liver enzymes.

This RMP also identified missing information about the effect of aliskiren:
- on pregnancy,
- in the paediatric population,
- in patients with severe renal dysfunction or with renovascular hypertension,
- on the reduction in cardiovascular morbidity and mortality,
- long-term use of the combination with inhibitors of the renin-angiotensin system or calcium channel blockers,
- long-term data in certain subgroups of patients (diabetics, those with a history of cardiovascular disease, etc.).

04.3 Prescription data

According to IMS data (moving annual total, summer 2013), 423,925 prescriptions were issued for RASILEZ. RASILEZ is in most cases prescribed for patients with hypertension (87% of prescriptions).

04.4 Therapeutic use[4,5,6]

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.

[4] Groupe de travail pour la prise en charge de l'hypertension de la Société Européenne d'Hypertension (ESH) et de la Société européenne de Cardiologie (ESC), J Hypertens 2007; 25: 1013-85.
[5] Mancia G, Laurent S, Agabiti-Rosei E et al. "Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document". J Hypertens 2009; 27: 2121-2158.
[6] Joint ESC Guidelines. The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). Eur Heart J, doi:10.1093/eurheartj/ehs092.

Place of RASILEZ:
Given the proven efficacy of aliskiren only on blood pressure and the absence of benefit in terms of cardiovascular prevention and an increased risk of hyperkalaemia, renal impairment and hypotension of aliskiren by comparison with placebo (ALTITUDE and ASTRONAUT studies), in patients treated jointly with another inhibitor of the renin-angiotensin system, aliskiren (RASILEZ) can be used only after the failure of the five other classes of antihypertensives (diuretics, CEI, ARB, calcium-channel blockers and beta blockers), used alone or in combination, and who are not being treated with another RAAS inhibitor (CEI or ARB).

05 TRANSPARENCY COMMITTEE CONCLUSIONS

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

05.1 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 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 renin-angiotensin-aldosterone system (RAAS) (ARB or an CEI),
- the confirmation of the absence of any benefit in terms of cardiovascular prevention in the ASTRONAUT study, together 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 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 m^2); its efficacy/adverse effects ratio in these patients therefore cannot be established.

For other patients, in view of:
- the antihypertensive effect of aliskiren, demonstrated over short periods in these patients,
- the absence of available long-term data for aliskiren,
- the absence any demonstrated efficacy for aliskiren in terms of morbidity and mortality,
- the safety profile of aliskiren,

the efficacy/adverse effects ratio for RASILEZ is modest.

◗ Aliskiren is an antihypertensive which must be reserved for use as a last resort in patients who are not controlled by any of the five classes of antihypertensives (alone or in combination) that

have demonstrated efficacy in terms of morbidity and mortality and who have not been treated with any other inhibitor of the renin-angiotensin system (CEI or ARB).

Taking account of these points, the Committee considers that the actual benefit of RASILEZ (aliskiren):

- **remains 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,**
- **is moderate in other patients, i.e. in patients who are not controlled despite the use of the aforementioned five classes, used alone or in combination with each other, and who have not been treated with any other RAAS inhibitor (CEI or ARB).**

05.2 Transparency Committee Recommendations

The Committee confirms that it does not recommend continued inclusion of this product on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in hypertensive patients treated with a combination already containing a renin-angiotensin system inhibitor (CEI or ARB) and at the dosage in the Marketing Authorisation.
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 for other patients.

◗ **Proposed reimbursement rate: 30%** only for hypertensive patients who are not controlled by any of the five classes of antihypertensives that have demonstrated efficacy in terms of morbidity and mortality (diuretics, CEI, ARB, calcium-channel blockers and beta blockers) who are not receiving an inhibitor of the renin-angiotensin-aldosterone system (CEI or ARB).

◗ **Packaging:** appropriate for the prescription conditions.

◗ **Committee's request:**
The Committee wishes to re-assess this dossier in one year on the basis of the collected safety data.