HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

27 May 2009

RASILEZ HCT 150 mg/12.5 mg, film-coated tablets
B/30 (CIP code: 392 151-6)

RASILEZ HCT 150 mg/25 mg, film-coated tablets
B/30 (CIP code: 392 152-2)

RASILEZ HCT 300 mg/12.5 mg, film-coated tablets
B/30 (CIP code: 392 153-9)

RASILEZ HCT 300 mg/25 mg, film-coated tablets
B/30 (CIP code: 392 154-5)

Applicant: NOVARTIS PHARMA SAS

Aliskiren / hydrochlorothiazide
ATC code: C09XA52

List I

Date of the Marketing Authorisations (centralised procedure): 16/01/2009

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Aliskiren / hydrochlorothiazide

1.2. 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."

1.3. Dosage
"The recommended dose of RASILEZ HCT is one tablet per day. RASILEZ HCT should be taken with a light meal once a day, preferably at the same time each day. Grapefruit juice should not be taken together with RASILEZ HCT. The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks.

Posology in patients not adequately controlled with aliskiren or hydrochlorothiazide monotherapy: Individual dose titration with each of the two components may be recommended before changing to the fixed combination. When clinically appropriate, 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. Dosing should be individualised and adjusted according to the patient's clinical response.

Posology 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.

Renal impairment: No adjustment of the initial dose is required for patients with mild to moderate renal impairment. Due to the hydrochlorothiazide component, RASILEZ HCT is contraindicated for use in patients with severe renal impairment (glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2).

Hepatic impairment: Thiazides should be used with caution in patients with impaired hepatic function. No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment. Due to the hydrochlorothiazide component, RASILEZ HCT is contraindicated in patients with severe hepatic impairment.

Elderly patients (over 65 years): No adjustment of the initial dose is required in elderly patients.

Paediatric patients: RASILEZ HCT is not recommended for use in children and adolescents below age 18 due to a lack of data on safety and efficacy."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

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

2.2. Medicines in the same therapeutic category

RASILEZ (aliskiren) 150 mg/day or 300 mg/day and ESIDREX (hydrochlorothiazide) 25 mg/day in separate doses.
No currently available medicinal product contains 12.5 mg of hydrochlorothiazide alone.

2.3. Medicines with a similar therapeutic aim

All medicinal products indicated in the treatment of essential hypertension: other antihypertensives that are prescribed as monotherapy or in combinations.

Other products consisting of fixed-dose combinations containing an ACE inhibitor, a calcium channel blocker, a sartan, a beta-blocker or a diuretic:

a. Angiotensin II receptor antagonist (AII RA) + diuretic:

candesartan 8 mg or 16 mg	+	HCTZ 12.5 mg:	COKENZEN, HYTACAND
eprosartan 600 mg	+	HCTZ 12.5 mg:	COTEVETEN
irbesartan 150 mg (or 300 mg)	+	HCTZ 12.5 mg (or 25 mg)	COAPROVEL
losartan 50 mg (or 100 mg)	+	HCTZ 12.5 mg (or 25 mg)	FORTZAAR, HYZAAR
olmesartan medoximil 20 mg	+	HCTZ 12.5 mg (or 25 mg)	ALTEIS DUO, CO-OLMETEC
telmisartan 40 mg or 80 mg	+	HCTZ 12.5 mg (or 25 mg)	MICARDISPLUS, PRITORPLUS
valsartan 80 mg or 160 mg	+	HCTZ 12.5 mg (or 25 mg)	COTAREG, NISISCO

b. AII RA + calcium channel blocker:

valsartan 80 mg/160 mg	+	amlodipine 5 mg/10 mg:	EXFORGE

c. ACE inhibitor + calcium channel blocker:

trandolapril 2 mg	+	verapamil 180 mg:	TARKA SR; OKADRIK SR.

d. ACE inhibitor + diuretic:

benazepril 10mg	+	HCTZ 12.5mg:	BRIAZIDE, CIBADREX
captopril 50 mg	+	HCTZ 25.0 mg:	CAPTEA, ECAZIDE, and G[1]
enalapril 20 mg	+	HCTZ 12.5 mg:	CO-RENITEC, and G
fosinopril 20 mg	+	HCTZ 12.5 mg:	FOZIRETIC
lisinopril 20 mg	+	diHCTZ 12.5 mg:	PRINZIDE, ZESTORETIC, and G
perindopril 2 mg (4 mg)	+	indapamide 0.625 mg (1.25 mg)	PRETERAX, BIPRETERAX
quinapril 20 mg	+	HCTZ 12.5 mg:	ACUILIX, KORETIC, and G
ramipril 5 mg	+	HCTZ 12.5 mg:	COTRIATEC
zofenopril 30 mg	+	HCTZ 12.5 mg:	ZOFENILDUO

e. calcium channel blocker + beta-blocker:

nifedipine 20 mg	+	atenolol 50 mg:	BETA-ADALATE, TENORDATE, and G

1 "G": generic products. See Afssaps Generics Register.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Seven studies have assessed the efficacy and safety of RASILEZ HCT (aliskiren + HCTZ):

- Four studies involved a comparison with one of the active substances (aliskiren or HCTZ) given as monotherapy;
- Three studies (2303, 2306[2] and 2344) involved an active comparator other than aliskiren or HCTZ (lisinopril and ramipril). The primary aim of these studies was not to assess efficacy and safety of the active substances in combination with HCTZ, and they will not be examined in this opinion.

In these seven studies, the primary endpoint was mean reduction in diastolic blood pressure (DBP) from baseline after 8 weeks of treatment; reduction in systolic blood pressure (SBP) was a secondary endpoint.

The dossier also includes two non-comparative studies, the primary objective of which was to assess safety (studies 2302 and 2302E1), and the results of which will not be presented in this opinion.

Studies in comparison with one of the active substances (aliskiren or HCTZ) given as monotherapy

A phase II study (2204[3]) compared aliskiren + HCTZ at various dosage levels with aliskiren (150 and 300 mg) or HCTZ (12.5 and 25 mg) given as monotherapy.

A phase III study (2309[4]) compared the efficacy of aliskiren 300 mg + HCTZ 25 mg versus placebo + HCTZ 25 mg in 487 obese hypertensive patients showing no response after 4 weeks of treatment with HCTZ 25 mg/day.

A phase III study (2332[5]) compared the efficacy of aliskiren 300 mg + HCTZ 12.5 or 25 mg versus aliskiren 300 mg in 718 hypertensive non-responders after 4 weeks of treatment with aliskiren 300 mg/day.

A phase III study (2333, unpublished) compared the efficacy of aliskiren 150 mg or 300 mg + HCTZ 25 mg versus HCTZ 25 mg in 872 hypertensive non-responders after 4 weeks of treatment with HCTZ 25 mg/day.

The design and main results of these four studies are presented in Table 1, which is appended to this opinion. A significant reduction in DBP was observed with aliskiren + HCTZ in comparison with the active substances given as monotherapies.

3.2. Adverse effects

According to the SPC, the safety of RASILEZ HCT has been assessed in 9 clinical trials involving more than 3,900 patients. The overall incidence of reported adverse effects involving RASILEZ HCT was comparable to that observed for placebo.

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2 Andersen K et al. “Comparative efficacy and safety of aliskiren, an oral direct renin inhibitor, and ramipril in hypertension: a 6-month, randomized, double-blind trial” Journal of hypertension 2008,26:589-99.

3 Villamil et al. ”Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide” Journal of hypertension 2007;25:217-26.

4 Jordan et al. ”Direct renin inhibition with aliskiren in obese patients with arterial hypertension” Hypertension 2007;49:1047-55.

5 Nickenig et al. ”Efficacy of aliskiren/hydrochlorothiazide single-pill combinations in aliskiren non-responders” Blood pressure 2008;17 (suppl 2):31-40.

The most commonly reported adverse event was diarrhoea, which was observed in 1.3% of patients receiving RASILEZ HCT.

3.3. Conclusion

RASILEZ HCT is a fixed-dose combination of aliskiren and hydrochlorothiazide, which is available in four dosage levels: 150 mg / 12.5 mg, 150 mg / 25 mg, 300 mg / 12.5 mg and 300 mg / 25 mg.

Efficacy and tolerance of these products have been assessed using four randomised controlled double-blind comparative studies (studies 2204, 2309 and 2332 and 2333).

In all of these studies, mean patient age was 55 years; one study involved patients aged over 65. These studies all involved patients with mild to moderate hypertension.

In these studies, after 8 weeks of treatment, a significant reduction in DBP was observed in those receiving aliskiren in combination with HCTZ in comparison with each active substance given as monotherapy.

The efficacy of the aliskiren + HCTZ combination has been demonstrated using a surrogate endpoint (reduction in diastolic blood pressure) but has not yet been demonstrated using a clinical endpoint involving morbidity and mortality.

These studies assessed the combination of aliskiren + HCTZ taken separately; no studies on the fixed-dose combination (RASILEZ HCT) are available. The usefulness of administering two antihypertensive drugs as a fixed-dose combination rather than separately has not been established.

The tolerance profile of aliskiren/HCTZ combinations did not differ, in these studies, from the known tolerance profiles of the two active substances. The most frequently observed adverse effect is diarrhoea (1.3%).

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Essential hypertension can be life-threatening, because of its complications.
These proprietary products come within the scope of preventive treatment.

The efficacy/adverse effects ratio of fixed-dose RASILEZ HCT combinations, assessed by measuring reduction in blood pressure, is high. These fixed-dose combinations have not been shown to have an effect in terms of reduction in morbidity and mortality.

RASILEZ (aliskiren alone) is used for second-line therapy.

In patients whose blood pressure is not adequately controlled by aliskiren 150 mg given as a second-line monotherapy, RASILEZ HCT 150 mg/12.5 mg can be used as a third-line therapy.
In patients whose blood pressure is not adequately controlled by hydrochlorothiazide 12.5 mg given as monotherapy, possible antihypertensive combinations are those that have demonstrated a benefit in terms of morbidity and mortality. The medicinal product RASILEZ HCT 150 mg/12.5 mg is therefore a third-line therapy.
If blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to a maximum of 300 mg/25 mg RASILEZ HCT daily.

These fixed-dose combinations of aliskiren and hydrochlorothiazide are also third-line therapies, to be given as substitution therapies to patients whose blood pressure is controlled and stable on aliskiren and hydrochlorothiazide taken separately at the same doses as the combination.

Public health benefit:
Essential hypertension and cardiovascular disease (for which hypertension is a significant risk factor) represent a significant public health burden.
Reducing the morbidity and mortality attributed to hypertension is a public health need (a priority identified in the GTNDO* and the Public Health Act).
However, existing treatments (including flexible combinations of aliskiren and hydrochlorothiazide) already help to meet this need.
There is no indication that these fixed-dose combinations have any added benefit (even in terms of increased compliance) over flexible combinations of the two active substances.
Consequently, RASILEZ HCT is not expected to benefit public health in this indication.
***** *GTNDO: National Technical Group for Defining Objectives (DGS-2003)*

There are many alternative medicinal products that have been shown to have an impact in terms of reduction in morbidity and mortality: diuretics, beta-blockers, calcium channel blockers (including amlodipine) and other renin-angiotensin system antagonists.

The actual benefit of RASILEZ HCT products is substantial.

4.2. Improvement in actual benefit (IAB)

RASILEZ HCT 150 mg/12.5 mg, 150 mg/25 mg, 300 mg/12.5 mg and 300 mg/25 mg fixed-dose combinations of aliskiren 150 or 300 mg and hydrochlorothiazide 12.5 or 25 mg provide no improvement in actual benefit (IAB V) in comparison with concurrent use of the two active substances taken separately.

4.3. Therapeutic use

Antihypertensive treatment aims to prevent the cardiovascular and renal complications of hypertension. The goal should be to normalise blood pressure. Diuretics, beta-blockers, calcium channel antagonists and renin-angiotensin system antagonists have been shown to reduce the occurrence of cardiovascular complications. For these reasons, national and international guidelines suggest that one of these treatments should be used in initial treatment for hypertension.

RASILEZ HCT 150 mg /12.5 mg is a third-line therapy which may only be prescribed, according to the marketing authorisation, to patients whose blood pressure is not adequately controlled with aliskiren 150 mg or hydrochlorothiazide 12.5 mg given as monotherapy. If blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to a maximum of 300 mg/25 mg RASILEZ HCT daily.

The Committee notes that the usefulness of a fixed-dose combination in the management of patients with hypertension, in comparison with separate doses of the two drugs, has not been established. These products are suitable for the management of patients whose blood pressure has been brought down to normal levels on treatment with the two active substances taken separately at the same dose.

These products are not suitable for the management of all patients.

4.4. Target population

The prevalence of diagnosed and/or treated hypertension in France appears to be between 6.5 and 7.4 million patients (HCSP data 2002 and CREDES 1999, extrapolated to the French population in 2003, THALES, CEMKA 2001).
However, the actual prevalence of hypertension could be higher than the prevalence of diagnosed and/or treated hypertension. The MONICA survey showed that only 52.2% of people with hypertension aged between 35 and 64 were aware of their hypertension.
If the MONICA data are extrapolated, and if we assume that only 52.2% of patients with hypertension are diagnosed and/or treated, the real prevalence of hypertension could be of the order of 12.5-14.2 million people in France.

For information, a study on treatment methods for hypertension in general practice (THALES/CEMKA 2001) showed that 49% of patients were treated with a monotherapy, 34% with a dual therapy, 13% with triple therapy and 4% with four or more agents.

No data are available concerning the percentage of patients in France who are treated with 150 or 300 mg aliskiren and 12.5 or 25 mg of hydrochlorothiazide and whose blood pressure is stable. Thus the target population of RASILEZ HCT cannot currently be estimated.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage levels given in the marketing authorisation.

Packaging: appropriate for the prescription conditions.

Reimbursement rate: 65%

***List of abbreviations**:*
ali: aliskiren (RASILEZ); amlo: amlodipine; ate: atenolol; HCTZ: hydrochlorothiazide; irb: irbesartan; pbo: placebo; ram: ramipril; val: valsartan

Table 1 "Summary of studies in comparison with one of the active substances given as monotherapy"

Studies	Design	Patients	Treatments	Results	Conclusion
2204	Phase II, randomised, double-blind, multifactorial, placebo- and HCTZ-controlled study (8 weeks). *Primary endpoint*: reduction in DBP ali versus pbo and ali+HCTZ versus HCTZ and versus ali	N = 2752 (ITT) Average age: 55 years 95 < DBP < 110 mmHg	ali 75* mg, n=183 ali 150 mg, n=183 ali 300 mg, n=180 HCTZ 6.25* mg, n=194 HCTZ 12.5 mg, n=188 HCTZ 25 mg, n=173 ali 75*/HCTZ 6.25, n=187 ali 75*/HCTZ 12.5, n=189 ali 75*/HCTZ 25, n=186 ali 150/HCTZ 6.25, n=173 ali 150/HCTZ 12.5, n=184 ali 150/HCTZ 25, n=187 ali 300/HCTZ 12.5, n=180 ali 300/HCTZ 25, n=173 Placebo, n=192	ali 150 vs pbo: -2.01 mmHg, 95% CI [-3.63; -0.39], p<0.0152 Ali 300 vs placebo: -3.33 mmHg, 95% CI [-4.95; -1.7] p<0.0001 ali 150/HCTZ 6.25: -3.42 mmHg (± 0.84), NS vs ali 150 and NS vs HCTZ 6.25 ali 150/HCTZ 12.5: -4.97 mmHg (± 0.83), p<0.0004 vs ali 150 and p=0.0314 vs HCTZ 12.5 ali 150/HCTZ 25: -5.71 mmHg (± 0.82), p<0.0001 vs ali 150 and p=0.0001 vs HCTZ 25 ali 300/HCTZ 12.5: -6.93 mmHg (± 0.83), p<0.0001 vs ali 300 and p<0.0001 vs HCTZ 12.5 ali 300/HCTZ 25: -7.33 mmHg (± 0.82), p<0.0001 vs ali 300 and p<0.0001 vs HCTZ 25	After 8 weeks of treatment: Significant reduction in DBP on aliskiren versus placebo p<0.0002 Significant reduction in DBP on aliskiren/HCTZ versus HCTZ and versus aliskiren alone, with the exception of the aliskiren 150/HCTZ 6.25 mg combination.
2309	Phase III, double-blind, randomised, placebo-controlled study (8 weeks). *Primary endpoint:* reduction in DBP on HCTZ 25/ali 300 mg versus HCTZ 25/placebo	N = 487 Average age: 54 years 90 < DBP < 110 mmHg *Obese patients*: Mean BMI 34± 4 kg/m² non-responders after 4 weeks of treatment with HCTZ 25 mg	HCTZ / ali, n=122 HCTZ / amlo, n=126 HCTZ / irb, n=119 HCTZ / pbo, n=120	HCTZ 25 / pbo: -7.89 mmHg (±0.73) **HCTZ 25/ali 300:** -11.91 mmHg (±0.74) Mean difference: -4.02, 95% CI = [-6.02; -2.01] p<0.0001	After 8 weeks of treatment: Significant reduction in DBP on HCTZ 25 / aliskiren 300 mg versus HCTZ 25 mg/placebo, p < 0.0001

Studies	Design	Patients	Treatments	Results	Conclusion
2332	Double-blind, randomised, ali/HCTZ versus ali phase III study (8 weeks). *Primary endpoint*: reduction in DBP on ali 300 mg / HCTZ 12.5 or 25 mg versus ali 300 mg	N = 872 Mean age: 55 years 95 < DBP < 110 mmHg non-responders after 4 weeks of treatment with ali 300 mg	ali 300* / HCTZ 12.5, n=292 ali 300* / HCTZ 25, n=284 ali 300*, n=296	ali 300* / HCTZ 12.5: -10.5 mmHg (± 0.5) ali 300* / HCTZ 25: -11 mmHg(± 0.6) ali 300*: -7.4 mmHg (± 0.5) Mean difference ali 300 / HCTZ 12.5 vs ali 300: -3.1, 95% CI = [-4.5; -1.7] ali 300 / HCTZ 25 vs ali 300: -3.6, 95% CI = [-5; -2.2] p<0.0001	After 8 weeks of treatment: Significant reduction in DBP on aliskiren 300 / HCTZ 12.5 and aliskiren 300 / HCTZ 25 versus aliskiren 300, p<0.0001
2333	Double-blind, randomised, ali / HCTZ versus HCTZ, phase III study (8 weeks). *Primary endpoint*: reduction in DBP on ali 150 or 300 mg / HCTZ 25 mg versus HCTZ 25 mg	N = 718 Average age: 54 years 95 < DBP < 110 mmHg Non-responders after 4 weeks of treatment with HCTZ 25 mg	ali 150 / HCTZ 25, n=242 ali 300* / HCTZ 25, n=232 HCTZ 25, n=244	ali 150 / HCTZ 25: -8.52 mmHg (± 0.47) ali 300* / HCTZ 25: -10.73 mmHg (± 0.48) HCTZ 25 -4.8 mmHg (± 0.47) Mean difference ali 150 / HCTZ 25 vs HCTZ 25: - 3.73, 95% CI [- 5.02, - 2.43] ali 300 / HCTZ 25 vs HCTZ 25: - 5.94, 95% CI [- 7.24, -4.63] p<0.001	After 8 weeks of treatment: Significant reduction in DBP on aliskiren 150 or 300 / HCTZ 25 versus HCTZ 25, p<0.0001

* the aliskiren 300 mg/day dose should only be prescribed for patients whose blood pressure is not controlled by the 150 mg/day dose.