HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

31 March 2010

EXFORGE HCT 5 mg/160 mg/12.5 mg, film-coated tablets
B/30 (CIP: 397 327-5)
B/56 (CIP: 397 328-1)
B/90 (CIP: 397 329-8)

EXFORGE HCT 10 mg/160 mg/12.5 mg, film-coated tablets
B/30 (CIP: 397 330-6)
B/56 (CIP: 397 331-2)
B/90 (CIP: 397 332-9)

EXFORGE HCT 5 mg/160 mg/25 mg, film-coated tablets
B/30 (CIP: 397 333-5)
B/56 (CIP: 397 334-1)
B/90 (CIP: 397 335-8)

EXFORGE HCT 10 mg/160 mg/25 mg, film-coated tablets
B/30 (CIP: 397 336-4)
B/56 (CIP: 397 337-0)
B/90 (CIP: 397 338-7)

Applicant: NOVARTIS PHARMA SAS

Amlodipine/valsartan/hydrochlorothiazide

ATC code: C09DX01

List I

Date of Marketing Authorisation: 16/10/2009

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance (boxes of 30 and 90) and approved for use by hospitals (boxes of 30, 56 and 90).

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Amlodipine (besylate)/valsartan/hydrochlorothiazide

1.2. Indication
“Treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlorothiazide (HCT), taken either as three single-component formulations or as a dual-component and a single-component formulation.”

1.3. Dosage
“The recommended dose of EXFORGE HCT is one tablet per day, to be taken preferably in the morning.

Before switching to EXFORGE HCT patients should be controlled on stable doses of the monocomponents taken at the same time. The dose of EXFORGE HCT should be based on the doses of the individual components of the combination at the time of switching to EXFORGE HCT.

The maximum recommended dose of EXFORGE HCT is 10 mg/320 mg/25 mg.

Special populations

Renal impairment

Due to the hydrochlorothiazide component, EXFORGE HCT is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min) (see sections 4.3 and 5.2 of the SPC). No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in patients with moderate renal impairment.

Hepatic impairment

Due to the hydrochlorothiazide and valsartan components, EXFORGE HCT is contraindicated in patients with severe hepatic impairment (see section 4.3 of the SPC). In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan and therefore EXFORGE HCT is not suitable for this group of patients (see sections 4.3, 4.4 and 5.2 of the SPC).

Heart failure and coronary artery disease

There is limited experience with the use of EXFORGE HCT, particularly in the maximum dose, in patients with heart failure and coronary artery disease. Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of EXFORGE HCT, 10 mg/320 mg/25 mg.

Elderly (age 65 years or over)

Precautionary measures including more frequent monitoring of blood pressure are recommended in elderly patients, particularly at the maximum dose of EXFORGE HCT, 10 mg/320 mg/25 mg, since the data available on this patient population are limited.

Paediatric population
There are no data on the use of EXFORGE HCT in the paediatric population (patients aged below 18 years) in the indication essential hypertension.

Method of administration
EXFORGE HCT can be taken with or without food. The tablets should be swallowed whole with some water, at the same time of day, preferably in the morning."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2009)
C : Cardiovascular system
C09 : Agents acting on the renin-angiotensin system
C09D : Angiotensin II antagonists, combinations
C09DX01 : Valsartan, amlodipine and hydrochlorothiazide

2.2. Medicines in the same therapeutic category
2.2.1 Comparator medicines:
These are comparator medicines and not active ingredients
The separate use of amlodipine 5 or 10 mg and valsartan 160 mg and hydrochlorothiazide (HCTZ) 12.5 or 25 mg.
There are no other fixed combination of angiotensin II receptor antagonists (sartans), calcium channel blockers and HCTZ.

2.3. Medicines with a similar therapeutic aim
All medicines indicated in the treatment of essential hypertension.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy
The evaluation of efficacy and tolerance is based on the results of three studies:
- two bioequivalence studies (VEA A2306 and VEA A2305) which demonstrated the bioequivalence of the combinations EXFORGE HCT (10/160/25) and (5/160/12.5) and their respective monotherapies in free combination using the kinetic parameters studied [C_{max}, AUC and t_{max}].
- a randomized, double-blind phase III study (VEA A2302) performed in 2,236 patients with moderate to severe essential hypertension who were followed up for 8 weeks. The aim of this study was to determine efficacy in terms of reduction in diastolic blood pressure (DBP) by comparison with baseline.

A phase II/III study (A2201) was also submitted. Since the aim of this study was to compare the efficacy of fixed combinations of valsartan and amlodipine in various dosages with the individual components in monotherapy, it will not be discussed in this opinion.

Finally, two open studies with descriptive results were submitted: study A2201E1 (open follow-up to the aforementioned study A2201) and study VEA ABR01.

3.1.1. Double-blind phase III study: study VEA A2302

Method: randomised, double-blind, 4-arm study (amlodipine 10/valsartan 320/HCTZ 25 mg, valsartan 320 mg/HCTZ 25 mg, valsartan 320 mg/amlodipine 10 mg and HCTZ 25 mg/amlodipine 10 mg) performed in 2,236 patients with moderate to severe hypertension who were followed up for 8 weeks.

Inclusion criteria: adult patients (18-86 years of age) with DBP of between 100 and 120 mmHg and SBP of between 145 and 200 mmHg.

Treatments:
- Amlodipine 10/valsartan 320/HCTZ 25 mg, n = 571
- Valsartan/HCTZ: 320/25 mg, n = 553
- Valsartan/amlodipine: 320/10 mg, n = 558
- HCTZ/amlodipine: 25/10 mg, n = 554

During the first two weeks of treatment, patients were treated with, respectively, amlodipine 5/valsartan 160/HCTZ 12.5 mg, valsartan 160/HCTZ 12.5 mg, valsartan 160/amlodipine 5 mg and HCTZ 12.5/amlodipine 5 mg. From the third week, doses were doubled (forced titration).

Note: In this study, the dose increase was made irrespective of the patients' blood pressure.

Primary endpoint: mean variation (reduction) in DBP and SBP (in mmHg) compared with baseline at 8 weeks.

RESULTS: ITT analysis (cf. Table 1).
On inclusion, the patients' characteristics were comparable.

Table 1: Mean variation in SBP and DBP (in mmHg) at 8 weeks.

Treatment	Inclusion Mean (SD)	Mean difference compared to baseline, mmHg (SD)	95% CI	Mean difference compared to triple therapy, mmHg (SD)	p
DBP					
V/H/A 320/25/10 mg N = 571	106.4 (5.08)	-24.57 (0.39)	[-25.34; -23.79]		
V/H 320/25 mg N = 553	106.2 (5.07)	-19.40 (0.43)	[-20.25; -18.55]	-5.05 (0.539)	<0.0001
V/H 320/10 mg N = 558	106.6 (5.14)	-21.4 (0.39)	[-22.18; -20.63]	-3.25 (0.537)	<0.0001
H/A 25/10 mg N = 554	107.1 (5.14)	-19.6 (0.40)	[-20.39; -18.80]	-5.28 (0.539)	<0.0001
SBP					
V/H/A 320/25/10 mg N = 571	169.6 (14.49)	-39.37 (0.69)	[-40.72; -38.00]		
V/H 320/25 mg N = 553	169.5 (13.81)	-31.81 (0.73)	[-33.26; -30.36]	-7.64 (0.84)	<0.0001
V/H 320/10 mg N = 558	169.6 (13.70)	-33.37 (0.66)	[-34.66; -30.07]	-6.18 (0.84)	<0.0001
H/A 25/10 mg N = 554	170.8 (14.25)	-31.87 (0.71)	[-33.26; -30.47]	-8.20 (0.84)	<0.0001

V = valsartan, H = HCTZ, A = amlodipine

After 8 weeks of treatment, a significantly larger reduction in DBP and SBP was observed with the combination valsartan 320/amlodipine 10/HCTZ 25 mg than with the combination

valsartan 320/HCTZ 25 mg, the combination valsartan 320/amlodipine 10 mg and the combination amlodipine 10/HCTZ 25 mg.

Note: The results of this study concern the combination amlodipine 10 mg/valsartan 320 mg/HCTZ 25 mg, a fixed combination for which the company is not requesting reimbursement.

3.1.2. Open studies

A2201E1
Method: open follow-up study to study A2201 comparing the efficacy of two tritherapies with valsartan/amlodipine/HCTZ in 1,237 patients followed up for 52 weeks.

Inclusion criteria: Patients under control at the end of study A2201 (SBP < 140 mmHg and DBP < 90 mmHg).

Treatments:
Eligible patients were randomized and treated with the combination valsartan 80/amlodipine 2.5 mg or valsartan 80/amlodipine 5 mg for a period of 4 weeks.

After 4 weeks of treatment, patients without symptomatic hypotension or peripheral oedema were treated (forced titration) with the combination valsartan 160/amlodipine 5 mg (n = 462) or valsartan 160/amlodipine 10 mg (n = 506).

In patients who were not under control (DBP ≥ 90 mmHg or SBP ≥ 140 mmHg), HCTZ 12.5 mg could be added to the treatment. This was done in 154 patients in the valsartan160/amlodipine 5 mg group and 115 patients in the valsartan 160/amlodipine 10 mg group).

Primary endpoint: Mean reduction in DBP at 52 weeks (descriptive analysis).

Results: cf. Table 2

Table 2: Mean reduction in DBP in mmHg at 52 weeks (SD)

	DBP on inclusion	Week 4	Week 52
V 160 /A 10	98.7 (3.2)	n = 506 -15.5 (6.7)	n = 426 -18.8 (6.8)
V 160/A 10/H 12.5	99.5 (3.5)	n = 115 -13.4 (7.1)	n = 106 -18.2 (8.1)
V 160/A 5	98.7 (3.2)	n = 462 -15.1 (6.8)	n = 406 -18.2 (7.1)
V 160/A 5/H 12.5	100.1 (3.7)	n = 154 -11.0 (6.9)	n = 142 -15.2 (7.3)

SD: standard deviation
V = valsartan, H = HCTZ, A = amlodipine

This table reflects the reductions in DBP observed in each treatment group. Given the methodology of this study its results are descriptive and must therefore be interpreted with caution.

VEA ABR01

Method: open, parallel-group randomised study comparing the efficacy of two tritherapies with valsartan/amlodipine/HCTZ in 182 patients uncontrolled by valsartan 160/HCTZ 12.5/amlodipine 5 mg who were followed up for 12 weeks.

Inclusion criteria: adult patients (more than 18 years of age) under stable antihypertensive treatment for at least two months and uncontrolled, defined as follows:

- SBP ≥ 140 mm Hg and/or DBP ≥ 90, in patients at low cardiovascular risk (with no organ damage and with at most one cardiovascular risk factor, excluding diabetes),
- SBP ≥ 130 mm Hg and/or DBP ≥ 85, in patients at medium cardiovascular risk (with no organ damage and with more than two cardiovascular risk factors, excluding diabetes),
- SBP ≥ 130 mmHg and/or DBP ≥ 80, in patients at high cardiovascular risk (organ damage and/or diabetic and/or with cardiovascular disease),

Treatments: During the pre-inclusion period patients were treated with valsartan 160/HCTZ 12.5 mg.
At the end of this period, uncontrolled patients were treated with valsartan 160/HCTZ 12.5/amlodipine 5 mg (n = 264) for **4 weeks**.
During weeks 4 to 8, uncontrolled patients were randomized to 2 groups and treated with valsartan 160/HCTZ 12.5/amlodipine 10 mg (n = 88) or valsartan 160/HCTZ 25/amlodipine 5 mg (n = 94).
During weeks 8 to 12, all uncontrolled patients were treated with valsartan 160/HCTZ 25/ amlodipine 10 mg (n = 138).

Primary endpoint: percentage of patients whose SBP and DBP was controlled at 8 weeks.
The target values to be achieved for SBP and DBP were determined according to patients' cardiovascular risk on inclusion:

- Patients at low risk (1 risk factor excluding diabetes and no impairment of the target organs): <140/90 mmHg,
- Patients at intermediate risk (≥ 2 risk factors excluding diabetes and no impairment of the target organs): < 130/85 mmHg,
- Patients at high risk (impairment of the target organs and/or type 2 diabetes and/or known cardiovascular disease): < 130/80 mmHg,

Results:
After 8 weeks of treatment, results are available for 138 patients treated with valsartan 160/ HCTZ 25/amlodipine 10 mg out of the 182 randomized. Of these, 29/66 patients (43.9%, 95% CI [31.74; 56.70]) in the group previously treated with valsartan 160/HCTZ 12.5/amlodipine 10 mg and 33/72 patients (45.8%, 95% CI [34.02; 58]) in the group previously treated with valsartan 160/HCTZ 25/amlodipine 5 mg were controlled.

In the group previously treated with valsartan 160 /HCTZ 12.5/amlodipine 10 mg, 11/20 patients (55% [31.53; 76.94]) at low risk, 10/19 patients (52.6%, [28.86; 75.55]) at intermediate risk and 8/27 patients (29.6%, [13.75; 50.18]) were controlled.

In the group previously treated with valsartan 160/HCTZ 25/amlodipine 5 mg respectively, 9/14 patients (64.3% [31.53; 87.24]) at low risk, 10/21 patients (47.6%, [25.71; 70.22]) at intermediate risk and 14/37 patients (37.8%, [22.46; 55.24]) were controlled.

Given the methodology of this study (open, descriptive study in which results according to risk levels are available only for a small number of patients and the missing data were excluded from the analysis), the results must be interpreted with caution.

3.2. Adverse events

In study VEA A2302, adverse events were observed in 263 patients (45.2%) in the group amlodipine 10/valsartan 320/HCTZ 25 mg, 253 patients (45.3%) in the group valsartan 320/HCTZ 25 mg, 254 patients (44.9%) in the group valsartan 320/amlodipine 10 mg and 271 patients (48.3%) in the group amlodipine 10/HCTZ 25 mg.

In study A2201E1, adverse events were observed in 134 patients (23.5%) in the group amlodipine 10/valsartan 160 mg, 13 patients (9.3%) in the group amlodipine 10/valsartan 160/HCTZ 12.5 mg, 67 patients (11.2%) in the group amlodipine 5/valsartan 160 mg and 14 patients (9.3%) in the group amlodipine 5/valsartan 160/HCTZ 12.5 mg and 67 patients (11.2%) in the group amlodipine 5/valsartan 160.

In study VEA ABR01, adverse events were observed in 35 patients (39.8%) in the group amlodipine 10/valsartan 160/HCTZ 12.5 mg and 24 patients (25.5%) in the group amlodipine 5/valsartan 160/HCTZ 25 mg.

The thresholds for recording adverse events were different in the various studies: ≥ 2% (study A3202 and ABR01, see Table 3) and ≥ 1% (study A2201E1, see Table 4).

Table 3: Percentage of patients who had adverse events with a frequency of ≥ 2%, studies A3202 and ABR01

	Dizziness	Peripheral oedema	Headache	Oedema
Study VEA A2302				
Amlodipine 10/valsartan 320/HCTZ 25 mg	5%	3.3%	1.5%	1%
Valsartan 320/HCTZ 25 mg	4.1%	0.4%	1.3%	0
Valsartan 320/amlodipine 10 mg	0.9%	6.2%	0.4%	2.3%
Amlodipine 10/HCTZ 25 mg	2%	7.3%	2.1%	2%
Study VEA ABR01				
Amlodipine 10/valsartan 160/HCTZ 12.5 mg	2.3%	35.2%	0	1.1%
Amlodipine 5/valsartan 160/HCTZ 25 mg	0	16%	1.1%	2.1%

Table 4: Percentage of patients who had adverse events with a frequency of ≥ 1% (study A2201E1)

	Dizziness	Peripheral oedema	Headache	Fatigue
Study A2201E1*				
Amlodipine 10/valsartan 160 mg	3.2%	11.6%	0.9%	1.6%
Amlodipine 10/valsartan 160/HCTZ 12.5 mg	1%	6.2%	-	1%
Amlodipine 5/valsartan 160 mg	1%	3.7%	0.8%	2.2%
Amlodipine 5/valsartan 160/HCTZ 12.5 mg	0.7%	4%	-	-

3.3. Conclusion

The dossier is based on two bioequivalence studies (VEA A2306 and VEA A2305) versus separate use, a phase III study versus bitherapies (VEA A2302) in patients with moderate to severe hypertension and two open support studies (VEABR01 and VEA 2201).

Bioequivalence was demonstrated between EXFORGE HCT 10/160/25 (study VEA A2306) and 5/160/12.5 (study VEA A2305) and their respective components in free combination using the kinetic parameters studied [Cmax, AUC and tmax].

In study VEA A2302, after 8 weeks of treatment a significantly larger reduction in DBP and SBP was observed with the combination valsartan 320/amlodipine 10/HCTZ 25 mg than with the combination valsartan 320/HCTZ 25 mg, the combination valsartan 320/amlodipine 10 mg and the combination amlodipine 10/HCTZ 25 mg.

The company is not requesting reimbursement for the dosage studied in this study (amlodipine 10 mg/valsartan 320 mg/HCTZ 25 mg).

The only data available for the dosages amlodipine 5/valsartan 160/HCTZ 25 mg and 10/160/12.5 are from the study VEA ABR01 and the study A2201E1 for the dosage 10/160/12.5. Given the methodology of these studies and, in particular, their descriptive nature, no conclusion can be drawn from these results.
The adverse effects most commonly observed with the combination amlodipine/valsartan/HCTZ during these studies were: peripheral oedema, dizziness, fatigue and headache.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit:

Essential hypertension can, through its complications, be life-threatening.

These medicinal products are intended as preventive treatments.

The efficacy/adverse effects ratio on the basis of the drop in blood pressure is high.

These fixed combinations have not shown any impact in terms of the reduction in morbidity and mortality.

These medicinal products are fourth-line medicines for adult patients whose blood pressure is adequately controlled by the combination of amlodipine, valsartan and hydrochlorothiazide.

There are many alternatives which have shown an impact in terms of a reduction in morbidity and mortality (diuretics, beta-blockers, calcium-channel blockers or other antagonists of the renin-angiotensin system).

Public health benefit:
The public health burden represented by essential hypertension and the cardiovascular diseases for which it is a risk factor is substantial.
The reduction in morbidity and mortality attributable to hypertension is a public health need (priority identified by GTNDO* and public health legislation).
However, existing treatments (including the free combination of amlodipine, valsartan and hydrochlorothiazide) are already helping to meet this need.
There is no argument in favour of any benefit of treatment with this fixed combination as compared to the free combination of these three active ingredients (also as regards compliance).
Consequently, the medicinal product EXFORGE HCT is not expected to offer any public health benefit in this indication.
***** GTNDO: National Technical Group for the Definition of Objectives (DGS-2003)

In the management of hypertension, it is important to be able to adapt the dosage of antihypertensives to the clinical situation of each patient and that patient's potential progress; EXFORGE HCT, a fixed combination of 3 antihypertensives, cannot meet this need despite the different dosages proposed.

The consequences of stopping treatment with a fixed combination of 3 antihypertensives are potentially more serious than those linked to stopping monotherapy or bitherapy; thus, there is likely to be more pronounced hypertensive rebound on stopping a tritherapy.

A prescribing bias in favour of patients with mild to moderate hypertension, which would lead to over-prescribing of EXFORGE HCT in these patients, is to be feared, given the ease of using a tritherapy in a single tablet.

The iatrogenic risk of EXFORGE HCT is increased by comparison with the monotherapies and bitherapies available, because of the fixed combination of three active ingredients.

Finally, the availability of EXFORGE HCT (a fixed combination of amlodipine, valsartan and HCTZ) in 4 different dosages when EXFORGE (a fixed combination of amlodipine and valsartan) is already available on the market in 3 dosages could lead to prescribing errors.

There are many alternative medications which allow fine-tuning of the dosage.

In view of these data, the Transparency Committee believes that the potential for misuse linked to the availability of EXFORGE HCT exceeds the expected benefits.

Consequently, the medical benefit offered by these medicinal products is considered insufficient for them to be paid for by National Health Insurance.

4.2. Transparency Committee recommendations

The Transparency Committee does not recommend inclusion on the list of medicines reimbursed by National Health Insurance (B/30 and B/90) and on the list of medicines approved for use by hospitals and various public services (B/30, B/90, B/56) in the new indication and at the dosages in the Marketing Authorisation.