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TRANSPARENCY COMMITTEE

OPINION

28 March 2012

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

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

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

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

Applicant: NOVARTIS PHARMA SAS

amlodipine/valsartan/hydrochlorothiazide
ATC code: C09DX01 (ANGIOTENSIN II ANTAGONISTS COMBINATIONS)

List I

Date of Marketing Authorisation: 16/10/2009

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance (B/30 and 90) and approved for hospital use (B/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 formulation 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.

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

Specific 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 in 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). The maximum recommended dose of valsartan is 80 mg in patients with mild to moderate hepatic impairment without cholestasis and as a result EXFORGE HCT is not suitable for this patient group (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 at 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)

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

Paediatric population
There is no relevant use of EXFORGE HCT in the paediatric population (patients under 18 years old) for the indication of essential hypertension.

Method and route 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 the day and preferably in the morning."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

C : cardiovascular system
C09 : medicinal products acting on the renin-angiotensin system
C09D : angiotensin II antagonists, combinations.
C09DX01 : valsartan + amlodipine + hydrochlorothiazide

2.2. Medicines in the same therapeutic category

Separate doses of amlodipine 5 or 10 mg and valsartan 160 mg and hydrochlorothiazide (HCT) 12.5 or 25 mg.
No other fixed combinations of angiotensin II receptor antagonists (sartans), calcium blockers and HCT exist.

2.3. Medicines with a similar therapeutic aim

All medicines indicated for the treatment of essential hypertension.

3. REVIEW OF COMMITTEE OPINIONS AND REGISTRATION CONDITIONS

Registration opinion of 31 March 2010

"Actual benefit: It is important to be able to adjust the dosage of antihypertensives drugs in treating hypertension according to each patient's clinical situation and potential changes; EXFORGE HCT, a fixed-dose combination of 3 antihypertensives drugs does not meet this need despite the different dosages offered.
The consequences of stopping treatment with a fixed-dose combination of 3 antihypertensives drugs are potentially more serious than those of stopping monotherapy or bitherapy and a more severe rebound hypertensive effect might be expected when treatment with a triple therapy is stopped.
It is feared a drift in prescription towards patients with mild to moderate hypertension which would lead to over-prescription of EXFORGE HCT in these patients because of the ease of use of triple therapy as a single tablet.
The iatrogenic risk of EXFORGE HCT is increased compared with available monotherapies and bitherapies because of the fixed-dose combination of three active ingredients.
Lastly, the availability of EXFORGE HCT (a fixed-dose combination of amlodipine, valsartan and HCT) as 4 different strenghts , in comparison with EXFORGE (a fixed-dose combination of amlodipine and valsartan) which is already available on the market as 3 doses, could generate prescribing errors.
There are many treatment alternatives for fine dose adjustment.
In view of these findings the Transparency Committee considers that the potential incorrect use arising from the availability of EXFORGE HCT is greater than the actual benefits.

> *Public health benefit*:
> The public health burden of essential hypertension and cardiovascular diseases, for which it is a risk factor, is high.
> Reduction in the morbidity and mortality attributable to hypertension is a public health need (a priority identified in the GTNDO * and the public health law).
> However, existing treatments (including the free combination of amlodipine, valsartan and hydrochlorothiazide) already help to meet this need.
> There is no evidence in favour of treatment with this fixed-dose combination offering benefit compared with the free combination of these three active ingredients (including compliance).
> As a result there is no expected public health benefit for EXFORGE HCT in this indication.
> ***** GTNDO: French National Technical Group for Objective Setting in Public Health (Directorate-General for Health-2003)

As a result, the actual benefit of these proprietary medicinal products is deemed to be insufficient for reimbursement by the French National Health Insurance Funds.

Improvement in Actual Benefit (IAB): not applicable.

Transparency Committee recommendations: The Transparency Committee does not recommend inclusion on the list of medicines refundable National Health Insurance (B/30 and B/90) and on the list of medicines approved for hospital use and various public services (B/30, B/90, B/56) in the indication and at the posologies stated in the Marketing Authorisation. »

4. ANALYSIS OF AVAILABLE DATA

The efficacy and safety of EXFORGE HCT is based on 3 studies considered by the committee in its first examination of these proprietary medicinal products in March 2010:

- a double-blind, randomised, phase III study (VEA A2302) conducted in 2236 patients with moderate to severe hypertension who were followed up for 8 weeks, the aim of which was to establish efficacy in terms of reducing diastolic blood pressure (DBP) compared with inclusion.
- two open descriptive studies were submitted: study A2201E1 and study VEA ABR01.

In support of its new application the company also submitted:

- the 3 periodic safety update reports (PSUR) covering the period from 30 April 2009 to 16 April 2011,
- proposed supportive measures for the use of the medicine,
- proposals to set up real life prescribing studies.

4.1. Efficacy

4.1.1. Double blind, phase III study: VEA A2302 study

Method: double-blind, randomised, 4 arm study (amlodipine 10/valsartan 320/HCT 25 mg, valsartan 320 mg/HCT 25 mg, valsartan 320 mg/amlodipine 10 mg and HCT 25 mg/amlodipine 10 mg) conducted in 2236 patients with moderate to severe hypertension, who were followed up for 8 weeks.
Inclusion criteria: adult patients (18 to 86 years old) with DBP between 100 and 120 mmHg and SBP between 145 and 200 mmHg.

Treatments:

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

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

Note: in this study, doses were increased independently of the patient's blood pressure.

Primary efficacy endpoint: mean change (fall) in DBP and SBP (in mmHg) at 8 weeks compared with baseline.

RESULTS: ITT analysis (see Table 1).
Patient characteristics were similar at baseline.

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

Treatment	Inclusion Mean (SD)	Mean difference from baseline mmHg (SD)	95% CI	Mean difference compared with 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/A 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/A 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 = HCT, A=amlodipine

After 8 weeks of treatment, a greater fall in DBP and SBP was found with the valsartan 320/amlodipine 10/HCT 25 mg combination than with the valsartan 320/HCT 25 mg combination, the valsartan 320/amlodipine 10 mg combination and the amlodipine 10/HCT 25 mg combination.

The results of this study relate to the combination *of amlodipine 10 mg/valsartan 320 mg/HCT 25 mg, a fixed-dose combination for which the company is not requesting reimbursement.*

4.1.2. Open studies

A2201E1

Method: open follow up study of study A2201 comparing the efficacy of two triple therapies of valsartan/amlodipine/HCT in 1,237 patients followed up for 52 weeks.

Inclusion criteria: patients controlled at the end of study A2201 (SBP <140mmHg and DBP <90 mmHg).

Treatments:

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

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

In patients who are not controlled (DBP ≥ 90 mmHg or SBP ≥ 140 mmHg), HCT 12.5 mg could be added to the treatment. This was carried out in 154 patients in the valsartan160/amlodipine 5 mg group and 115 patients in the valsartan 160/amlodipine 10 mg group).

Primary efficacy endpoint: mean fall in DBP at 52 weeks (descriptive analysis).

Results: see table 2

Table 2: mean fall in DBP at 52 weeks in mmHg

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

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

This table shows the fall in DBP found by treatment group. In view of the methodology of this study its results are descriptive and must therefore be interpreted with caution.

VEA ABR01

Method: open, randomised, parallel groups study comparing the efficacy of two triple therapies of valsartan/amlodipine/HCT in 182 patients not controlled by valsartan 160/HCT 12.5/amlodipine 5 mg followed up for 12 weeks.

Inclusion criteria: adult patients (over 18 years old) on stable antihypertensive therapy for at least two months and not controlled, defined as:

- SBP ≥ 140 mmHg and/or DBP ≥ 90, in patients at low cardiovascular risk (without organ damage and no more than one cardiovascular risk factor excluding diabetes),
- SBP ≥ 130 mmHg and/or DBP ≥ 85, in patients at moderate cardiovascular risk (without 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 diabetes and/or cardiovascular disease),

Treatments: Patients were treated with valsartan 160/HCT 12.5 mg during the pre-inclusion period.

At the end of this period, the uncontrolled patients were treated with valsartan 160/HCT 12.5/amlodipine 5 mg (n=264) for **4 weeks**.

During weeks 4 to 8, patients who were not controlled were randomised into 2 groups and treated with valsartan 160/HCT 12.5/amlodipine 10 mg (n= 88) or valsartan 160/HCT 25/amlodipine 5 mg (n=94).

During weeks 8 to 12, all uncontrolled patients were treated with valsartan 160/HCT 25/amlodipine 10 mg (n=138).

Primary efficacy endpoint: percentage of patients controlled for SBP and DBP at 8 weeks.
Target SBP and DBP values were established according to the patient's cardiovascular risk at inclusion:

- Low risk patients (1 risk factor excluding diabetes and no end organ damage): <140/90 mmHg,
- Patients at intermediary risk (≥ 2 risk factors excluding diabetes and no end organ damage): < 130/85 mmHg,
- High risk patients (end organ damage and/or type 2 diabetes and/or overt cardiovascular disease): < 130/80 mmHg.

Results:

After 8 weeks of treatment results were available for 138 patients treated with valsartan 160/HCT 25/amlodipine 10 mg out of the 182 randomised patients. Of these, 29/66 patients (43.9%, 95% CI [31.74; 56.70]) in the group previously treated with valsartan 160 /HCT 12.5/amlodipine 10 mg and 33/72 patients (45.8%, 95% CI [34.02; 58]) in the group previously treated with valsartan 160/HCT 25/amlodipine 5 mg were controlled.
In the group previously treated with valsartan 160/HCT 12.5/amlodipine 10 mg, respectively, 11/20 of the low risk patients (55% [31.53; 76.94]), 10/19 of the intermediary risk patients (52.6%, [28.86; 75.55]) and 8/27 of the high risk patients (29.6%, [13.75; 50.18]) were controlled.
In the group previously treated with valsartan 160/HCT 25/amlodipine 5 mg, respectively, 9/14 of the low risk patients (64.3% [31.53; 87.24]), 10/21 of the intermediary risk patients (47.6%, [25.71; 70.22]) and 14/37 of the high risk patients (37.8%, [22.46; 55.24]) were controlled.

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

4.2. Adverse effects

4.2.1. Clinical study data

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

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

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

The thresholds for adverse event recording varied between these studies: ≥ 2% (study A3202 and ABR01, see table 3) and ≥ 1% (study A2201E1, see table 4).

Table 3: Percentage of patients with adverse events at an incidence of ≥ 2%, studies A3202 and ABR01

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

Table 4: Percentage of patients with adverse events at an incidence ≥ 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/HCT 12.5 mg	1%	6.2%	-	1%
amlodipine 5/valsartan 160 mg	1%	3.7%	0.8%	2.2%
amlodipine 5/valsartan 160/HCT 12.5 mg	0.7%	4%	-	-

4.2.2. PSUR data

The analysis of the last three periodic safety update reports (PSUR) covering the period from 30 April 2009 to 16 April 2011 provides an estimate of patient treatment-exposure of more than 300,000 patient-years.
During this period, 471 safety reports were submitted of which 87 were medically confirmed as serious (44 unlisted). The most commonly reported adverse drug reactions were cardiovascular, particularly oedema, hypotension, hypertension, dysrhythmias, atrial fibrillation, one heart failure and one myocardial infarction. Two deaths were reported during this period: no relationship of causality conclusions are available.

In the last PSUR, 3 new signals were identified: haemolytic anaemia, rhabdomyolysis and angle-closure glaucoma.

The analysis of these findings did not change the tolerance profile of these proprietary medicinal products and the only change made to the SPC during this period involved an amendment to the storage conditions.

4.3. Measurements to support use of the medicine

In order to reduce potential incorrect use in the prescribing of EXFORGE HCT, a fixed-dose combination of three active ingredients, the pharmaceutical company proposes to introduce supportive measures for the use of the medicine:
- a restriction of reimbursement to initial prescription by a specialist in order to reduce a possible drift towards prescription to patients with mild to moderate hypertension.
- a communication campaign among prescribers emphasising the indication in which EXFORGE HCT may be used as substitution, production of an *aide mémoire* for dosages and a means of rapidly identifying the 3 active substances contained in the proprietary medicinal product.
- the availability of a card for each patient to whom EXFORGE HCT is prescribed showing the 3 active ingredients contained in each tablet.

4.4. Study programme

The pharmaceutical company is proposing a study programme in collaboration with the INSERM of Bordeaux:
- one study with the objective of assessing compliance and cardiovascular events in hypertensive patients treated with triple therapy from data available in the EGB (general practitioner's sample of French National Health Insurance beneficiaries). Therefore, a feasibility study has been carried out by the Bordeaux pharmacology department and a protocol has been drawn up.
- an EXFORGE HCT prescription monitoring study of which the aim would be to identify any incorrect use of the proprietary medicinal product and to assess compliance over a follow-up period of 2 years: the pharmaceutical company proposes to submit the results of this study 4 years after the product marketing launch A protocol has been drawn up for this.

The feasibility study proposed by the pharmaceutical company has been assessed and a summary is shown in the appendix.

The pharmaceutical company proposes two draft study protocols (synopsis) based on the EGB data to answer the questions about the impact of compliance on the incidence of cardiovascular events in patients treated with triple antihypertensive therapy and the impact of EXFORGE HCT treatment on improving treatment compliance; as these are not the final protocols the Committee cannot make any statement about their contents.

4.5. Conclusion

EXFORGE HCT (amlodipine/valsartan/HCT) has been assessed in a double blind randomised study compared with bitherapies combining 2 of the 3 active ingredients in EXFORGE HCT (VEA A2302) in 2236 patients with moderate to severe hypertension.
After 8 weeks of treatment, the fall in DBP and SBP was greater with the combination of valsartan 320/amlodipine 10/HCT 25 mg than with the combination of valsartan 320/HCT 25 mg, the combination of valsartan 320/amlodipine 10 mg and the combination of amlodipine 10/HCT 25 mg.
Note that the pharmaceutical company is not requesting reimbursement for the dosage examined in this study (amlodipine 10 mg/valsartan 320 mg/HCT 25 mg).

The only data available for the dosages, amlodipine 5/valsartan 160/HCT 25 mg and 10/160/12.5 are those from study VEA ABR01 and study A2201E1 for the 10/160/12.5 dosage. In view of the methodology of these studies and particularly their descriptive nature, no conclusions can be drawn from these results. There is therefore no appropriate data on the amlodipine 5/valsartan 160/HCT 25 mg and 10/160/12.5 mg dosages.

The most commonly reported adverse events with the amlodipine/valsartan/HCT combination in these studies were: peripheral oedema, dizziness, fatigue and headaches.

The analysis of the last three periodic safety update reports (PSUR) covering the period from 30 April 2009 to 16 April 2011 provides an estimate of patient treatment exposure of more than 300,000 patient-years. A total of 471 adverse events were reported during these periods including 87 medically confirmed serious events and two deaths (no conclusions on a relationship of causality are available on these). The most commonly reported adverse events were cardiovascular (oedema, hypotension, hypertension, and dysrhythmia including atrial fibrillation, heart failure and myocardial infarction).

The pharmaceutical company is proposing measures to facilitate correct use of the medicine:
- restriction of reimbursement to the initial prescription by a specialist,
- a communication campaign among prescribers and patients to alert them on the presence of three active ingredients in a same tablet.

It is also proposing to monitor prescriptions in order to assess compliance, the incidence of cardiovascular events and any incorrect use in hypertensive patients treated with triple therapy.

The Committee considers that:

- a fixed triple therapy of antihypertensives drugs only affects a limited proportion of severe hypertensive patients requiring specialist management. The lack of flexibility in adjusting treatment and dosage inherent to this fixed triple therapy makes it even more important that these patients are initially managed by specialists in hypertension (cardiologists and nephrologists).
- possible lack of knowledge about the active ingredients contained in EXFORGE HCT and about their doses by the patient and/or caregivers may impact both on the consequences of stopping treatment and on possible therapeutic interactions with other medicines taken concomitantly.
- The indication for this triple therapy must be limited to patients who are stable and whose blood pressure is sufficiently well controlled by a free combination of each of the active ingredients (as three monotherapies or a fixed bitherapy and a monotherapy) at the same doses. Treatment must not be prescribed to patients in other stages of the treatment strategy.

5. TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

Because of its complications, essential hypertension can be life-threatening.

These proprietary medicinal products are a preventative treatment.
The efficacy/tolerance ratio based on the fall in blood pressure values is high.

These fixed-doses combinations have not been shown to have an impact in terms of reducing morbidity or mortality.

These medicinal products are last line medicines in adult patients whose blood pressure is sufficiently controlled and stabilised with a combination of amlodipine, valsartan and hydrochlorothiazide, taken separately.

Numerous alternatives have been shown to have an impact in terms of reducing morbidity and mortality (diuretics, beta blockers, calcium channel blockers or other renin-angiotensin system antagonists).

Public health benefit:
The public health burden of essential hypertension and cardiovascular diseases, for which it is a risk factor, is high. The burden with respect to patients who may benefit from this proprietary medicinal product is low in view of their very limited number.
Reduction in morbidity and mortality attributable to hypertension is a public health need (a priority identified in the GTNDO * and the public health law).
However, existing treatments (including the free combination of amlodipine, valsartan and hydrochlorothiazide) already help to meet this need.
There is no evidence that treatment with this fixed–doses combination offers benefit over the free combination of the three active ingredients (including compliance issues).
The proprietary medicinal product EXFORGE HCT would not therefore be expected to have an impact on morbidity and mortality or quality of life.
As a result there is no expected public health benefit for the proprietary medicinal product EXFORGE HCT in this indication.

* GTNDO: French National Technical Group for Objective Setting in Public Health (Directorate-General for Health-2003).

The concerns expressed by the Transparency Committee in its opinion of 31 March 2010 have been taken into account by the pharmaceutical company, which has proposed to set up supportive measures for the use of the proprietary medicinal products EXFORGE HCT including, in particular, a real life prescribing study.

As these fixed triple therapies are for severely hypertensive patients, the Committee considers that the actual benefit offered by these proprietary medicinal products is only high in stable patients whose blood pressure is sufficiently controlled with the free combination association of each of the three active ingredients (as three monotherapies or a fixed bitherapy and a monotherapy) at the same doses, managed initially by a hypertension specialist (cardiologists and nephrologists).
The actual benefit will be reassessed within 2 years based on the results of a monitoring study under actual conditions of use (see study request in paragraph 5.5.2.).

5.2. Improvement in actual benefit (IAB)

EXFORGE HCT, a fixed-dose combination of amlodipine, valsartan and hydrochlorothiazide, does not offer an improvement in benefit (IAB V) compared with the joint use of each of its three components taken separately at the same doses.

5.3. Therapeutic use[1]

Antihypertensive therapy is intended to prevent the cardiovascular and renal complications of hypertension. The aim is to restore normal blood pressure values. Diuretics, beta blockers, calcium channel blockers and renin-angiotensin system antagonists have been shown to reduce the incidence of cardiovascular complications. For these reasons, national and international guidelines propose that hypertensive therapy be started with one of these medicines.

EXFORGE HCT is a last line medicine for the treatment of hypertension which is reserved for adult patients whose blood pressure is sufficiently controlled and stabilised with an combination of amlodipine, valsartan and hydrochlorothiazide taken separately. The utility of this fixed –dose combination in the management of patients compared with separate dosing with the three medicines has not been established.
In addition, this proprietary medicinal product is not suitable for the management of all patients.

5.4. Target population

The prevalence of hypertension in mainland France is estimated to be approximately 14 million adult patients throughout France as a whole. The prevalence estimate in the general population is based on an extrapolation of data from several studies, the most recent of which are ENNS (BEH 2008[2]) and the MONA LISA study 2005-2007.[3]

For information, an unpublished study on the methods of managing hypertension in general practice (THALES/CEMKA 2010) showed that:
- only 77% of patients are treated:
- 44% of patients are treated with low dose monotherapy or bitherapy, 34% with bitherapy, 17% with triple therapy and 5% with quadruple therapy or more.
- among patients treated with triple therapy, 3.6% or approximately 66,000 patients are treated with triple therapy including a calcium blocker, an ARB and a diuretic.
- the number of patients treated with triple therapy involving a combination of valsartan/amlodipine/HCT, is estimated to be 42,390 patients (including 2,900 patients treated with EXFORGE HCT).

According to EGB data extrapolated to the French population[4], 47,682 patients have at least one co-prescription of valsartan 160 mg, amlodipine 5 or 10 mg and hydrochlorothiazide

1 Working Group for the treatment of hypertension and the European Hypertension Society (ESH) and European Society for Cardiology (ESC) Journal of hypertension 2007; 25: 1013-85.
2 Mean blood pressure and prevalence of hypertension in 18 to 74 year old adults, ENNS 2006-2007. BEH thématique 49-50/16 December 2008: 478
3 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.

4 EGB is a representative sample of people with National Health Insurance in France. It contains anonymised information about reimbursed services, demographic features of beneficiaries and LTC since 2003. EGB data were extrapolated through the French population by calculating an extrapolation coefficient. The extrapolation coefficient was obtained from the number of beneficiaries in the EGB on 01/01/2011 (n = 594,370) as a proportion of the population of France on 01/01/2011 (n = 65 001 181). The calculated extrapolation coefficient was 1/109.36.

12.5 or 25 mg as three components alone or as a fixed-dose combination in 2011 (95% confidence interval 43,208 to 52,156).
We do not however have data allowing us to estimate the percentage of patients whose blood pressure is sufficiently controlled and stabilised with a combination of amlodipine, valsartan and hydrochlorothiazide.
Overall, the target population for EXFORGE HCT will be extremely small and less than 50,000, although this number cannot be accurately quantified.

5.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance (B/30 and B/90) and on the list of approved medicines for hospital use and various public services (B/30, B/90, B/56) in the indication and the posologies of the Marketing Authorisation.

5.5.1. Prescribing and reimbursement conditions

For reimbursement of these proprietary medicinal products, the committee recommends that their initial prescription be restricted to specialists in hypertension (cardiologists and nephrologists).

5.5.2. Request for study

The Committee has decided that this approval is subject to a post-registration study being carried out.
There are uncertainties about possible incorrect use under the actual conditions of use of this fixed –dose combination (and about consequences of this on the patient], particularly in terms of inappropriate prescription (dosage, patients suffering from non-severe hypertension or severe hypertension but not stabilised on the free combination of the 3 active ingredients).
In addition, the consequences of poor patient compliance with EXFORGE HCT treatment (particularly if doses are forgotten) could be more severe than those of a free triple therapy.
In addition, doubts remain about the potential improvement in compliance which may be achieved with EXFORGE HCT.
Uncertainties therefore exist about the benefit of this fixed-dose combination for patients.

The Committee has therefore asked for a follow-up study to be set up in patients treated for hypertension with EXFORGE HCT or with a free triple combination (including the bitherapy + monotherapy combination) using treatments belonging to the 3 therapeutic classes of antihypertensives drugs involved [diuretic, calcium blocker, renin-angiotensin system agent], including, in particular, patients on free triple therapy with the three active ingredients (INN) contained in EXFORGE HCT (amlodipine, valsartan and hydrochlorothiazide).

This study should provide a description in particular of,
- the features of treated patients [including socio-demographic data, severity level of the hypertension, previous treatments, particularly for hypertension, degree of stabilisation of the hypertension on these treatments] and the prescribing details [information on dosages, duration of treatment, area of specialisation of the prescriber including general practitioner]
- cardiovascular events, deaths, treatment drop-outs (and their reasons) occurring during the follow-up.
- treatment compliance by patients and modifications/ adaptations of the prescription by the doctor during follow-up.
- care resources used (hospitalisation, consultations, etc.).

This analysis should provide an estimate of the impact of using this fixed-dose combination compared with a free triple combination in terms of compliance, morbidity and mortality and even care resource use.

The patient follow-up period is to be two years. The Committee would like to emphasise that it wishes to reassess this proprietary medicinal product within a period of 2 years in light of the results of this study, which will be available at that point (i.e. data on patients at inclusion and the interim follow-up results). A subsequent assessment will be performed on the final results.

5.5.3. Packaging: appropriate for the prescription conditions.

5.5.4. Reimbursement rate: 65%

EXFORGE HCT
Preliminary study from the EGB

The aim of this study was to **identify the target population for EXFORGE HCT in 2010** and **to establish the feasibility of the two studies based on the EGB**:

- one design to evaluate the impact on the compliance of patients treated with triple or high level antihypertensive therapy on the incidence of cardiovascular events (CVA and myocardial infarction) in patients who have not previously had any of these events at inclusion (the period from January 2007 to December 2010) before EXFORGE HCT is marketed;
- the other, after EXFORGE HCT has been included for reimbursement, to assess the correct use of EXFORGE HCT by identifying the previous antihypertensive treatments taken prior to prescription of EXFORGE HCT, the subsequent changes in the antihypertensive prescription and the change in compliance in the year after starting EXFORGE HCT compared with the year before starting treatment (by calculating the Medication Possession Ratio (MPR)).

Only the results of the preliminary study on the target population are available.

The methodology for the preliminary study was as follows:

- Data were extracted from the EGB on 17 June 2011.
- Patients with hypertension in 2010 were identified from all those patients with the following characteristics:
    - Alive as of 31 December 2010,
    - 18 years old or older on 1 January 2010,
    - Included in the EGB no later than 31 March 2010,
    - Who had received at least one reimbursement for care since 2001,
    - Who had received at least one reimbursement for case since 2010.
- Patients with hypertension were defined by 3 criteria which identified 3 study populations:
    - Patients with LDD 12 (severe hypertension);
    - Patients (without LDD 12) who had been hospitalised between 2007 and 2009 with a primary related or associated diagnosis of hypertension (PMSI data);
    - Patients (without LDD 12 or hospitalisation with a main related or associated diagnosis of hypertension) who had been dispensed an antihypertensive at least once in 2010 (defined by their ATC classes: C02, C03, C07, C08, C09A, C09C, C09X).
- The description of antihypertensive dispensing in 2010 was obtained from the dates and the ATC codes.
- The results were extrapolated to the general adult French population by multiplying the numbers in the EGB by an extrapolation coefficient calculated from the ratio of the number of 18 year olds and older French people from INSEE data on 1 January 2010 to the number of people holding French National Health Insurance who were 18 years old or older in the EGB (coefficient = 122.16).

Main study results:

96,430 patients were identified as having hypertension:

- 12,044 patients were LDD 12 (12.5%);
- 18,674 patients (without LDD 12) had been hospitalised between 2007 and 2009 with a main, related or associated diagnosis of hypertension (19.4%);
- 65,712 patients (without LDD 12 or hospitalisation with a main, related or associated diagnosis of hypertension) who had been dispensed an antihypertensive at least once in 2010 (68.1%).

Most of these patients were women (56.7%). Average patient age in 2010 was 65.7 years old (± 14.7) and 2.5% of the patients died in 2010.

Patients with LDD 12 or a hospitalisation with a diagnosis of hypertension were on average older and more had other LDD s (particularly cardiovascular risk factors and co-morbidities).
0.5% of all of the patients identified as having hypertension in the EGB had been co-dispensed at least one of the 3 INN contained in EXFORGE HCT in 2010 (i.e. 498 patients). These included 1.5% of the patients with LDD 12, 0.5% of patients who had been hospitalised with a diagnosis of hypertension and 0.3% of patients who were treated with antihypertensives in 2010 (without LDD or hospitalisation).
11% of patients were co-dispensed at least one of the medicinal products in the 3 classes contained in EXFORGE HCT in 2010 (10,652 patients).
After extrapolating the data to the French population, the number of patients treated simultaneously with the 3 active ingredients in EXFORGE HCT was estimated to be 60,836 patients in 2010.
The population of patients treated simultaneously with the three ATC classes representing the three INN contained in EXFORGE HCT® was 1.3 million people.

Conclusion:
The minimum population liable to treated with EXFORGE HCT in France in 2010 is estimated to be 60,000 patients.
This feasibility study shows that the EGB contains a sufficient number of hypertensives treated with triple therapy to enable the studies proposed in the initial audit programme to be carried out.