HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

9 March 2011

TAREG 40 mg, film-coated tablet
B/30 (CIP code: 381 540-6)
B/56 (CIP code: 381 541-2)
B/90 (CIP code: 381 543-5)

TAREG 80 mg, film-coated tablet
B/30 (CIP code: 381 546-4)
B/56 (CIP code: 381 547-0)
B/90 (CIP code: 381 549-3)

TAREG 160 mg, film-coated tablet
B/30 (CIP code: 381 552-4)
B/56 (CIP code: 381 553-0)
B/90 (CIP code: 381 555-3)

Applicant: NOVARTIS PHARMA SAS

valsartan
ATC code: C09CA03
List I

Dates of initial Marketing Authorisations (mutual recognition, reference member state: Sweden):
TAREG 40 mg, film-coated tablet: 23 January 2006
TAREG 80 and 160 mg, film-coated tablet: 31 May 2001

Date of extension of the paediatric indication: 9 June 2010

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance (B/30 and B/90 pack sizes only) and approved for hospital use in the extension of indication: “treatment of hypertension in children and adolescents aged 6 to 18 years of age”.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

valsartan

1.2. Indications

Tablet form

"Hypertension:
Treatment of essential hypertension in adults (TAREG 80 and 160 mg only).
Treatment of hypertension in children and adolescents aged 6 to 18 years of age.

Recent myocardial infarction:
"Treatment of clinically stable in adults patients with symptomatic heart failure (HF) or asymptomatic left-ventricular systolic dysfunction (LVSD) after a recent (12 hours-10 days) myocardial infarction.

Heart failure:
Treatment of symptomatic heart failure in adults when angiotensin-converting enzyme (ACE) inhibitors cannot be used or in combination with an ACE inhibitor when beta-blockers cannot be used."

1.3. Dosage

"Children and adolescents aged 6 to 18 years"
The recommended starting dose is 40 mg once daily for children weighing less than 35 kg and 80 mg once daily for children weighing 35 kg or over. The dose should be adjusted according to the blood pressure response. The maximum doses studied in clinical trials are listed in the table below.
Doses higher than those listed below have not been studied and are therefore not recommended.

Body weight	Maximum dose investigated in clinical trials
≥ 18 kg to < 35 kg	80 mg
≥ 35 kg to < 80 kg	160 mg
≥ 80 kg to ≤ 160 kg	320 mg

Children less than 6 years of age
Available data are described in sections 4.8, 5.1 and 5.2 of the SmPC. However, the safety and efficacy of TAREG in children aged 1 to 6 years old have not been established.

Use in paediatric patients aged 6 to 18 years old with renal impairment
Use in paediatric patients with a creatinine clearance < 30 ml/min and paediatric patients undergoing dialysis has not been studied. Consequently, valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance > 30 ml/min. Renal function and serum potassium must be closely monitored (see sections 4.4 and 5.2 of the SmPC).

Use in paediatric patients aged 6 to 18 years old with hepatic impairment
As in adults, TAREG is contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3, 4.4 and 5.2 of the SPC). There is limited clinical experience with the use of TAREG in paediatric patients with mild to

moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

Paediatric heart failure and recent myocardial infarction
TAREG is not recommended for the treatment of heart failure or recent myocardial infarction in children below the age of 18 years old due to the lack of data on safety and efficacy."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

C : Cardiovascular system
C09 : Agents acting on the renin-angiotensin system
C09C : Angiotensin II antagonists
C09CA : Angiotensin II antagonists, plain
C09CA03 : Valsartan

2.2. Medicines in the same pharmaco-therapeutic category:

Other sartans indicated in the treatment of hypertension in children and adolescents aged 6 to 18 years old: losartan (COZAAR and generics), not currently refundable.

2.3. Medicines with a similar therapeutic aim

All other classes of antihypertensives suitable for use in children and adolescents:
- Diuretics: furosemide (LASILIX and generics) and spironolactone (ALDACTONE, SPIROCTAN and generics)
- ACE inhibitors: captopril (LOPRIL and generics), enalapril (RENITEC and generics), lisinopril (PRINIVIL, ZESTRIL and generics),
- Calcium-channel blockers: amlodipine (AMLOR and generics),
- Beta-blockers: acebutolol (SECTRAL and generics).

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

For this application for extension of the indication, the company has submitted six studies:

- 3 studies on patients aged 6 to 18:
  - o study A2302, the objectives of which were firstly to determine efficacy according to the dose administered and secondly to assess the efficacy and safety of valsartan compared to placebo in terms of effect/dose and maintenance of the reduction of SBP over a short period (2 weeks),
  - o study K2302, the objective of which was to determine the efficacy and safety of valsartan compared to enalapril in terms of the reduction of SBP after 12 weeks,
  - o study K2302E1 (extension phase of study K2302), the objective of which was to assess the long-term (14 to 66 weeks) efficacy and safety of valsartan alone or in combination with enalapril.

- 3 studies on patients less than 6 years old (A2307 and K2303 and its extension phase K2303E1). According to the SPC, "the efficacy and the safety of TAREG in children aged 1 to 6 years of age have not been established", and consequently the indication for patients aged under 6 years of age was not included in the marketing authorisation. Consequently, these studies will not be further examined in this opinion.

These studies were mainly conducted on patients with essential hypertension; only a small number of patients with secondary hypertension were included. This means that the specific efficacy of valsartan in cases of secondary hypertension cannot be established.

3.1.1. Study A2302, versus placebo

Methodology: phase III study conducted on 245 hypertensive patients aged 6 to 16 years of age in two phases:
Phase1: randomised, double-blind study of the dose-effect response phase in which three doses of valsartan tablets (low dose, medium dose and high dose[1]) were assessed for 2 weeks.
Phase2: randomised, double-blind comparative study with valsartan tablets versus placebo (2 weeks).

Treatments (phase2):
The patients were randomised into 2 groups: valsartan at the dose defined on the basis of their weight during the first study phase or placebo, and monitored for 2 weeks:
- valsartan tablet (low, medium and high dose), n=123,
- placebo, n=122.

Inclusion criteria: patients aged 6 to 16 years old weighing over 20 kg with hypertension defined as SBP ≥ 95th percentile for age, sex and height.

Primary efficacy endpoint: for phase 2
Maintenance of the SBP observed at the end of phase1.

1 Patients <35 kg: low dose= 10 mg/d, medium dose = 40 mg/d and high dose = 80 mg/d
Patients >35kg: low dose= 20 mg/d, medium dose = 80 mg/d and high dose = 160 mg/d

RESULTS: Intention-to-treat analysis (see Table 1).
At inclusion, the patients' characteristics were comparable.

Table 1: Variation in SBP 2 weeks after the end of period 1.

	Valsartan tablet n=123	Placebo n=122	P versus placebo
End of period 1			
Mean SBP mmHg (SD)	122.2 (12.07)	**122.2 (11.51)**	
End of period 2			
Mean SBP mmHg (SD)	123.3 (13.05)	126.1 (12.09)	
Mean variation (SD)	**1.2 (9.42)**	3.9 (9.66)	**0.03**
[95% CI]	**[-0.52 ; 2.84]**	[2.15 ; 5.61]	

After two weeks of treatment, a significant difference in SBP was observed between the valsartan tablet and placebo groups: variation in SBP of 1.2 (9.42) mmHg with valsartan versus 3.9 (9.66) mmHg with placebo, p=0.03. These results need to be interpreted with caution because of the short follow-up period (two weeks), and there is no guarantee of long-term efficacy.

3.1.2. Study K2302, versus active comparator: enalapril

Methodology: randomised, double-blind non-inferiority comparative study with valsartan versus enalapril performed on 296 hypertensive patients aged 6 to 17 years old who were monitored for 12 weeks.
Non-inferiority was accepted if the lower limit of the confidence interval of the difference in variation in SBP did not exceed a limit set at -3.5 mmHg. The analysis was carried out on a per-protocol basis.

Treatments:
The patients were randomised into two groups (*per-protocol* population):
- valsartan tablet, n= 107,
- enalapril tablet, n= 115.

The doses were stratified according to the patients' weight:
- patients weighing 18 to 35 kg: valsartan 80 mg or enalapril 10 mg,
- patients weighing 35 to 80 kg: valsartan 160 mg or enalapril 20 mg,
- patients weighing over 80 kg: valsartan 320 mg or enalapril 40 mg,

Inclusion criteria: patients aged 6 to 17 weighing between 18 kg and 160[2] kg with hypertension defined as SBP ≥ 95th percentile for age, sex and height.

Primary efficacy endpoint: variation in SBP after 12 weeks compared to the baseline.

RESULTS: Intention-to-treat and *per-protocol* analysis (see Table 2).

At inclusion, the patients' characteristics were comparable (statistical analysis not available) except for distribution by:
- gender: 43% of girls in valsartan group versus 29.5% in enalapril group,
- age: 45% of patients aged 6 to 12 years old in valsartan group versus 36.9% in enalapril group.

2 The eventual average weight of patients on inclusion was 65.8 kg.

Table 2: Variation in SBP after 12 weeks

	Valsartan tablet	Enalapril tablet
At inclusion Mean SBP mmHg (SD)	134 (9.83)	**134.6 (9.28)**
After 12 weeks: ITT Mean SBP mmHg (SD) Mean variation (SD) Difference vs. enalapril [95% CI]	N=148 121 (13.96) **-** 15.4 (11.29) -1.3 [-3.8 ; 1.17]	N=148 122.8 (13.38) -14.1 (11.28)
After 12 weeks: PP Mean variation (SD) Difference vs. enalapril [95% CI]	N=107 **-16(1.57)** **-1 [-3.87 ; 1.82]**	N=115 **-15 (1.56)**

After 12 weeks of treatment, an average reduction of SBP of 16 mmHg was observed in the valsartan group versus 15 mmHg in the enalapril group (difference -1 mmHg, 95% CI [-3.87; 1.82]); as the lower limit of the confidence interval of the difference observed was -3.87 points, below the limit set in the protocol (-3.5 mmHg), the non-inferiority of valsartan compared to enalapril was established.

3.1.2. Study K2302E1, extension phase of study K2302

This study was conducted on 250 hypertensive patients aged 6 to 17 years old with or without chronic renal failure (CRF) who had taken part in study K2302 and had followed up to 66 weeks. Patients not suffering from CRF continued to receive valsartan at the dose assigned in the main study (K2302) and patients with CRF received a combination of valsartan + enalapril, with doses were determined according to their weight.
Consequently, the patient distribution was as follows:

- 212 patients without CRF: valsartan, n=103 and enalapril, n=109,
- 38 patients with CRF: valsartan, n=21 and enalapril, n=17,

Results:
At the end of the extension period, in patients without CRF, efficacy in terms of reduction of SBP was maintained in the valsartan and enalapril groups and was not statistically different between the two groups: -11.6 mmHg (9.74) and -10.2 (9.7), NS.

In patients with CRF, the reduction of SBP was significantly higher in the valsartan + enalapril group than in enalapril + placebo group: -23.6 mmHg (10.79) versus -18.2 mmHg (9.51), p=0.03.

3.2. Adverse effects

A total of 37 adverse effects were observed in study A2302 (19 in period 1 and 20 in period 2). The most frequent adverse effects were:

- headaches: 8 (3.1%) in period 1 and 5 (2%) in period 2,
- orthostatic hypotension: 1 (0.4%) and 2 (0.8%).

A total of 31 adverse effects were observed in study K2302 (10.4%), 16 in the valsartan group versus 15 in the enalapril group. The most frequent adverse effects were:

- headaches: 2 versus 6,
- abdominal pains: 2 versus 0,
- vertigo: 2 versus 3,
- nausea: 2 versus 0,
- vomiting: 2 versus 0.

A total of 39 adverse effects were observed in study K2302E1 (15.6%): 6 in the valsartan group, 6 in the enalapril group, 9 in the valsartan + enalapril group, 3 in the enalapril + placebo group. The most frequent adverse effects were:

- headaches: 3 versus 3 versus 2 versus 0,
- hyperkalaemia: 0 versus 2 versus 7 versus 2,
- hypotension: 0 versus 0 versus 3 versus 0.

According to the SPC, the most frequent events are vertigo, orthostatic hypotension, renal failure and impairment.

3.3. Conclusion

The efficacy and tolerance of valsartan in children and adolescents aged 6 to 18 years old with hypertension alone have been assessed in two studies: a 2-week placebo-controlled study (A2302) and a 12-week study versus active comparator (K2302).

In study A2302, after two weeks of treatment, a significant difference in SBP was observed between the valsartan tablet and placebo groups: variation in SBP of 1.2 (9.42) mmHg with valsartan versus 3.9 (9.66) mmHg with placebo, p=0.03. These results need to be interpreted with caution because of the short follow-up period (two weeks), and there is no guarantee of long-term efficacy.

In study K2302, after 12 weeks of treatment, an average reduction of SBP of 16 mmHg was observed in the valsartan group versus 15 mmHg in the enalapril group (difference -1 mmHg, 95% CI [-3.87; 1.82]); as the lower limit of the confidence interval of the difference observed was below the limit set in the protocol (-3.5 mmHg), valsartan was accepted as being not inferior to enalapril.

In study K2302E1, at the end of the extension period, in patients without CRF, efficacy in terms of reduction of SBP was maintained in the valsartan and enalapril groups and was not statistically different between the two groups: -11.6 mmHg (9.74) and -10.2 (9.7), NS.
In patients with CRF, the reduction of SBP was significantly higher in the valsartan + enalapril group than in the enalapril + placebo group: -23.6 mmHg (10.79) versus -18.2 mmHg (9.51), p=0.03.

In these children and adolescents with hypertension, valsartan has not, to date, shown any benefit in terms of morbidity and mortality.

The adverse events most frequently reported were headache, abdominal pain, vertigo, nausea, vomiting, hyperkalaemia, hypotension, renal failure and impairment.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Hypertension in children and adolescents is a serious condition which can be life-threatening, either immediately or as a result of complications.

The efficacy of valsartan in this extension of indication to hypertensive children and adolescents has been demonstrated for an intermediate criterion (reduction of SBP). A small number of patients with secondary hypertension have taken part in studies; consequently, the specific efficacy of valsartan in cases of secondary hypertension cannot be clearly established. No morbidity/mortality data are available.

The efficacy/adverse effects ratio of valsartan in this indication is high.

These proprietary medicinal products are preventive treatments.

Taking into account the efficacy data available and the lack of long-term tolerance data, TAREG proprietary medicinal products (valsartan) are second-line medicinal products for children and adolescents aged 6 to 18 years old with essential hypertension.

There are alternatives treatments available for this indication, in particular losartan (COZAAR and generics, not currently refundable) and some diuretics, calcium-channel blockers, beta-blockers and ACE inhibitors.

> Public health benefit:
> Hypertension in children is a disease with serious consequences.
> However, the public health burden can be considered as minor since this condition is rare in children.
> Reducing morbidity and mortality attributable to hypertension is a public health need, particularly in children, which is part of the established priorities (GTNDO*, Public Health Act**, Paediatric Pharmaceutical Products).
> However, the existing treatments already help to meet this need.
> On the basis of the data available from the clinical trials [in particular, demonstration of non-inferiority versus enalapril], this proprietary medicinal product is not expected to have an impact on morbidity and mortality or quality of life.
> Consequently, TAREG is not expected to benefit public health in this indication in children.
> ** GTNDO: Groupe Technique National de Définition des Objectifs [National Technical Objective Definitions Group] (DGS-2003)*
> *** Public Health Act 2004: Act no. 2004-806 of 9 August 2004 on public health policy*

The actual benefit of TAREG (valsartan) in children and adolescents aged 6 to 18 years of age with essential hypertension is substantial.

4.2. Improvement in actual benefit (IAB)

TAREG offers no improvement in actual benefit (IAB V) in treatment strategy of the essential hypertension in children aged 6 to 18 years old.

4.3. Therapeutic use[3,4]

It is important to distinguish between secondary hypertension and essential hypertension in children and adolescents.

Secondary hypertension has a range of aetiologies: endocrine, particularly adrenal; renal, due to abnormalities of the parenchyma or stenosis of the renal artery; or cardiovascular, due to coarctation of the aorta or constitutional vascular disease. It can be extremely severe and sometimes malignant. Treatment primarily focuses on addressing the cause when it is possible, and the only role of antihypertensive treatment is to stabilise patients before aetiological treatment is administered, or to correct any residual hypertension if treatment is not sufficiently effective, or to substitute aetiological treatment where this cannot be provided.

Essential hypertension is not very common in children and adolescents. As in adults, hypertension) is generally well tolerated and only exposes patients to the risk of complications, especially cardiovascular complications, in the long term.
It is diagnosed on the basis of the principle that blood pressure increases with age, gender and weight. The blood pressure of these patients is therefore measured using an algorithm taking these criteria into account. Hypertension in children and adolescents is defined as SBP above the 95th percentile for an individual of the patient's age, gender and weight.

Diet and lifestyle measures, including physical exercise and limiting the consumption of sugar, saturated fatty acids and salt, are recommended as the first-line approach for all hypertensive children and adolescents irrespective of their blood pressure, with or without drug treatment as well.

The decision to introduce drug treatment must take into account the patient’s blood pressure but also whether or not target organs have been damaged and whether or not the patient presents other cardiovascular risk factors and associated forms of comorbidity such as obesity, renal damage and diabetes.

Consequently, drug treatment is recommended for patients with:
- symptomatic hypertension,
- hypertension and target organ damage,
- secondary hypertension,
- hypertension associated with type 1 or 2 diabetes.

Beta-blockers and ACE inhibitors have been clearly established as effective in controlling hypertension in children and adolescents, while the clinical data available for calcium-channel blockers is limited and data relating to ARA-II drugs is relatively recent. Most practitioners therefore offer beta-blockers and ACE inhibitors as first-line treatment.

Valsartan has been found to be effective in respect of an intermediate criterion: the reduction of SBP in children and adolescents aged 6 to 18 years old with essential hypertension. Valsartan may be offered as second-line treatment in view of the efficacy data available and the lack of long-term safety data.

4.4. Target population

The target population for valsartan in this indication is children and adolescents aged 6 to 18 years old with essential hypertension. It can be estimated on the basis of the following factors:

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3 Management of high blood pressure in children and adolescents : recommendations of the European Society of Hypertension. Journal of Hypertension 2009,27:1719-42.
4 The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004:555-576

According to Deschênes[5], the prevalence of hypertension in children has never been specifically studied but probably only affects a few hundred individuals. As of 31/12/2009 there were 504 children and adolescents aged 5 to 19 years old being treated for a LDD (Long Duration Disease) 12 (severe hypertension) under the general sickness insurance scheme.
As the general sickness insurance scheme covers almost 80% of people eligible for National Health Insurance benefits, it is estimated that around 650 children and adolescents in France are being treated for a LDD condition 12.

Consequently, the target population for valsartan in hypertensive children and adolescents aged 6 to 18 years old can be estimated at approximately 1,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance (B/30 and B/90 pack sizes only) and on the list of medicines approved for hospital use and various public services (B/30, B/56 and B/90 pack sizes) in the extension of indication "Treatment of hypertension in children and adolescents aged 6 to 18 years old" and at the dosage of the Marketing Authorisation.

Packaging: Appropriate for prescribing conditions.

Reimbursement rate: 65%

5 Deschênes G. Diagnostic de l'hypertension artérielle de l'enfant. [Diagnosis of hypertension in children] EMC (Elsevier Masson SAS, Paris), Pédiatrie, 4-078-G640, 2008.