HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

9 March 2011

TAREG 3 mg/ml oral solution
B/1 160 ml (CIP code: 491 474-8)

Applicant: NOVARTIS PHARMA SAS

valsartan
ATC code: C09CA03

List I

Date of Marketing Authorisation (mutual recognition, reference member state: Sweden): 17 June 2010

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
valsartan

1.2. Indication
"Treatment of hypertension in children and adolescents aged 6 to 18 years of age."

1.3. Dosage
"For children who are unable to swallow tablets, the use of the TAREG oral solution at doses up to 80 mg valsartan (corresponding to 27 ml) is recommended.

The systemic exposure and peak plasma concentration of valsartan are higher with the oral solution compared to the tablets.

The initial dosage for the TAREG oral solution is 20 mg (corresponding to 7 ml of the solution) once daily for children below 35 kg of weight and 40 mg (corresponding to 13 ml of the solution) once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response up to a maximum dose of 80 mg valsartan (corresponding to 27 ml of the solution).

It is not recommended to switch between TAREG tablets and TAREG oral solution unless clinically required as there is insufficient information to guide an appropriate dose on switching between the two formulations. Indirect comparisons suggest that the oral bioavailability of valsartan with the solution is approximately twice folded higher than the tablets form.

Therefore, if switching from TAREG tablets to TAREG oral solution is considered essential on clinical grounds, the valsartan dose should be adjusted as described in the table below and blood pressure should be carefully monitored. The dose should be titrated based on blood pressure response and tolerability.

Tablets	Solution	
Valsartan dose	Valsartan dose to provide when switching	Volume to take:
40 mg	20 mg	7 ml
80 mg	40 mg	13 ml
160 mg	80 mg	27 ml
320 mg	Due to the high volume of solution that would be necessary, the use of the solution is not recommended	Not applicable

If switching from TAREG oral solution to TAREG tablets is considered clinically essential, the same initial dose in milligrams should be given. Subsequently, frequent blood pressure monitoring should be performed taking into account potential under-dosing and the dose should be titrated further based on blood pressure response and safety.

Children less than 6 years of age
Available data are described in sections 4.8, 5.1 and 5.2 of the SmPC. However, 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 SmPC). 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 and adolescents below the age of 18 years old due to the lack of data on safety and efficacy.

Method of administration
TAREG may be taken with or without food. It must be taken with a glass of water."

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 of age : 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).

Only LASILIX and SECTRAL are available in oral solution form.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

For this application for extension of the indication, the company has submitted six studies, all conducted on the tablet form:

- 3 studies on patients aged 6 to 18:
  - study A2302, the objectives of which were firstly to determine efficacy according to the dose administered and secondly to assess the efficacy and of valsartan compared to placebo in terms of effect/dose and maintenance of the reduction of SBP over a short period (2 weeks),
  - 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,
  - 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 of age (A2307 and K2303 and its extension phase K2303E1). According to the SPC, "the efficacy and safety of TAREG in children aged 1 to 6 years of age have not been established", and consequently the indication for patients aged less than 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.

Two bioequivalence studies have also been carried out specifically on the "oral solution" form:

- Study A2301, which compared valsartan tablet with valsartan oral solution prepared extemporaneously on kinetic parameters [Tmax, $T_{1/2}$, Cmax and AUC]. This study showed Cmax to be 32% higher for the tablet form than for the oral solution form, with similar AUC values.
- Study K2101, which compared the oral solution marketed form of valsartan to the oral solution prepared extemporaneously and which investigated kinetic parameters [Tmax, $T_{1/2}$, Cmax and AUC]. This study showed the bioavailability of the oral suspension to be better than the placebo.

The oral solution's SmPC states that "systemic exposure and peak plasma concentration of valsartan are higher with the oral solution compared to the tablets. It is not recommended to switch between TAREG tablets and TAREG oral solution unless clinically required as there is insufficient information to guide an appropriate dose on switching between the two formulations. Indirect comparisons suggest that oral bioavailability of valsartan is approximately twice fold higher than the tablets form."

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:
Phase 1: 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.

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

Phase 2: randomised, double-blind comparative study with valsartan tablets versus placebo (2 weeks).

Treatments (phase 2):
The patients were randomised into 2 groups: valsartan at the dose defined on the 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 phase 1.

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,

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

Inclusion criteria: patients aged 6 to 17 years old 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.

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 in 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 of age 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 were given a combination of valsartan + enalapril, with doses 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 valsartan + enalapril group than in enalapril + placebo group: -23.6 mmHg (10.79) versus -18.2 mmHg (9.51), p=0.03.

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

3.2. Adverse effects

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

- headache: 8 (3.1%) in period 1 and 5 (2%) in phase 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 safety of valsartan in children and adolescents aged 6 to 18 years of age 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 valsartan + enalapril group than in 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.

As all the studies were conducted on the tablet form, and the results of bioequivalence studies suggest that the bioavailability of valsartan solution is about twice that of the tablet form, the SmPC states that "It is not recommended to switch between TAREG tablets and TAREG oral solution unless clinically required as there is insufficient information to guide an appropriate dose on switching between the two formulations."

The efficacy/adverse effects ratio of TAREG oral solution (valsartan) in children and adolescents aged 6 to 18 years old with essential hypertension is high.

This proprietary medicinal product is a preventive treatment.

Taking into account the efficacy data available and the lack of long-term safety data, TAREG oral solution (valsartan) is a second-line medicinal product for children and adolescents aged 6 to 18 years old with essential hypertension.

There are alternative treatments available for this indication, in particular losartan (COZAAR and generics, not currently reimbursed) 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, it is not expected that this proprietary medicinal product will have an impact on morbidity/mortality and 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 oral solution in the treatment of essential hypertension among children and adolescents aged 6 to 18 years of age who are unable to swallow tablets is substantial.

4.2. Improvement in actual benefit (IAB)

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

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 etiologies: 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's 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 an etiological 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.

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

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 who are unable to swallow tablets. It can be estimated on the basis of the following factors:

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 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.

It is difficult to quantify the proportion of these patients who are unable to swallow film-coated tablets.

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 hospital use and various public services in the 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.