HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 October 2010

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

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

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

Applicant: NOVARTIS PHARMA SAS

valsartan
ATC code: C09CA03

List I

Dates of first Marketing Authorisation (national):
TAREG 40 mg : 23 /01/2006
TAREG 80 et 160 mg : 31/05/2001

Date of extension of the indication: 16 February 2009

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use in the extension of the indication “treatment of symptomatic heart failure when Angiotensin-Converting Enzyme (ACE) inhibitors cannot be used or as add-on therapy to ACE inhibitors when beta-blockers cannot be used”.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Valsartan

1.2. Indications
"Hypertension**:**
Treatment of essential hypertension.

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

Heart failure:
Treatment of symptomatic heart failure when Angiotensin-Converting Enzyme (ACE) inhibitors cannot be used or as add-on therapy to ACE inhibitors when beta-blockers cannot be used."

1.3. Dosage
"Heart failure: The recommended starting dose of TAREG is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done at intervals of at least two weeks to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.
Valsartan may be administered with other heart failure therapies. However, the triple combination of an ACE inhibitor, a beta-blocker and valsartan is not recommended.
Evaluation of patients with heart failure should always include assessment of renal function.

Method of administration: TAREG may be taken independently of a meal and should be taken with water.

Additional information on special populations:
Elderly: No dose adjustment is required in elderly patients.

Renal impairment: No dose adjustment is required for patients with a creatinine clearance > 10 ml/min.

Hepatic impairment: In patients with mild to moderate hepatic impairment without cholestasis, the dose should not exceed 80 mg. TAREG is contraindicated in patients with severe hepatic impairment and patients with cholestasis.

Paediatric population: TAREG is not recommended for use in children below the age of 18 years due to a lack of data on tolerance 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, plain
C09CA : Angiotensin II antagonists, plain
C09CA03 : Valsartan

2.2. Medicines in the same therapeutic category:

The following other sartans are indicated in the treatment of symptomatic heart failure:

- Candesartan (ATACAND, KENZEN), indicated in the "Treatment of NYHA class II and III heart failure with left-ventricular systolic dysfunction (LVEF ≤ 40%): if angiotensin-converting enzyme (ACE) inhibitors are not tolerated or as add-on therapy to ACE inhibitors in patients who remain symptomatic under ACE inhibitor therapy. This indication is based on the results of the CHARM-Alternative and CHARM-Added trials"
- Losartan (COZAAR), indicated in the "Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with angiotensin-converting enzyme (ACE) inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left-ventricular ejection fraction ≤ 40% and should be clinically stable and on an established treatment regimen for heart failure": *indication not listed for reimbursement.*

2.3. Medicines with a similar therapeutic aim

All other medicines indicated in the management of heart failure.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

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

- three studies (103, 104 and 106), the objective of which was to determine the efficacy and tolerance of valsartan versus placebo and lisinopril (in one study) in terms of haemodynamic parameters and exercise-test performance, carried out over short periods (4 to 16 weeks),
- one study, the objective of which was to evaluate the efficacy of valsartan as add-on therapy to an optimal standard therapy (OST) for heart failure versus placebo in terms of morbidity/mortality (VaL-HeFT study[1]) in patients followed up for an average of 23 months.

In view of the objectives and duration of studies 103, 104 and 106, only the results of the morbidity/mortality study (VaL-HeFT) are detailed in this Opinion.

VaL-HeFT study

Objective: To evaluate the efficacy and tolerance of valsartan 160 mg twice daily as add(on therapy to an optimal standard therapy (OST) versus placebo in terms of the reduction in all-cause mortality and major cardiovascular events in heart failure patients.
The OST included the following substances: diuretics (in 85% of patients), beta-blockers (35%) and ACE inhibitors (92%).

Method: Placebo-controlled randomised double-blind phase III study in 5010 patients with stable NYHA class II, III or IV heart failure followed up for 24 months.

Treatments:

- Valsartan 160 mg twice daily + OST, n = 2511,
- Placebo + OST, n = 2499.

Inclusion criteria: Adults aged 18 years and over with a clinical history of heart failure within the past three months:

- with clinically stable NYHA class II, III or IV heart failure,
- left-ventricular dysfunction (LVEF ≤ 40%) and left-ventricular dilatation,
- who had been treated for at least the past two months with optimised standard therapy including ACE inhibitor, diuretic, digoxin and beta-blocker.

Primary endpoints: Two endpoints were defined:

- all-cause mortality,
- occurrence of the first major cardiovascular event, composite endpoint comprising: all-cause mortality, resuscitated cardiac arrest, hospitalisation due to heart failure, intravenous administration of an inotropic or vasodilator drug for at least 4 hours without hospitalisation.

Secondary endpoints, in particular the components of the composite primary endpoint: All-cause mortality, resuscitated cardiac arrest, hospitalisation due to heart failure, intravenous administration of an inotropic or vasodilator drug for at least 4 hours without hospitalisation.

[1] Cohn JN et al. A randomized trial of the angiotensin-receptor blocker valsartan on chronic heart failure. N Engl J Med 2001; 345: 1667-75.

RESULTS: Intention-to-treat analysis (see Table 1).
On inclusion, the patients' characteristics were comparable.
Concomitant treatments were as follows:

- 93% of patients were being treated with ACE inhibitors at the following average doses: 17 mg of enalapril, 19 mg of lisinopril, 80 mg of captopril, 6 mg of ramipril and 23 mg of quinalapril,
- 35% of patients were being treated with beta-blockers: patients were stratified according to whether they were using beta-blockers.
- 5% of patients were being treated with spironolactone.

Table 1: Number and percentage of cardiac events observed after a median follow-up period of 23 months

	Valsartan 160 mg 2× + OST n = 2511	Placebo + OST N = 2499	Relative risk [95% CI]	p
All-cause mortality	**495 (19.7%)**	**484 (19.4%)**	**1.02 [0.90; 1.15]**	**NS**
First major cardiovascular event:	**723 (28.8%)**	**801 (32.1%)**	**0.87 [0.79; 0.96]**	**0.009**
- All-cause mortality	427 (17%)	419 (16.8%)	1.01 [0.88; 1.6]	NS
- Hospitalisation due to HF	349 (13.9%)	463 (18.5%)	0.73 [0.63; 0.83]	< 0.001
- Resuscitated cardiac arrest	20 (0.8%)	30 (1.2%)	0.65 [0.37; 1.15]	NS
- Intravenous administration of an inotropic or vasodilator drug for at least 4 hours without hospitalisation	7 (0.3%)	8 (0.3%)	0.89 [0.32; 2.47]	NS

After an average follow-up period of 23 months, no significant difference in all-cause mortality was observed: 495/2511 patients (19.7%) in the valsartan + OST group versus 484/2499 patients (19.4%) in the placebo + OST group, RR 1.02 [0.90; 1.15].
A significant reduction in the second, composite primary endpoint (all-cause mortality, resuscitated cardiac arrest, hospitalisation due to heart failure, intravenous administration of an inotropic or vasodilator drug for at least 4 hours without hospitalisation) was observed in the valsartan 160 mg 2× daily + OST group compared with the placebo + OST group: 723 events versus 801, RR 0.87 [0.79; 0.96], p = 0.009.

This result is mainly due to the reduction in hospitalisations for heart failure, which accounted for 53% of the total events observed.

3.2. Adverse effects

In the VaL-HeFT study, 159 patients (6.3%) in the valsartan + OST group versus 86 patients (3.5%) in the placebo group discontinued treatment on account of adverse events, p < 0.001.
The most frequent adverse events (> 2%) were:

- dizziness: 442 patients (17.6%) vs. 226 (9.1%)
- hypotension: 242 patients (9.7%) vs. 109 (4.4%)
- renal impairment: 98 patients (3.9%) vs. 40 (1.6%)
- asthenia: 51 patients (2%) vs. 36 (1.4%)
- diarrhoea: 49 patients (2%) vs. 25 (1%)
- hyperkalaemia: 90 patients (3.6%) vs. 26 (1%) (increase in serum potassium of 0.12 mg/dl vs. 0.07 mg/dl, p < 0.001)
- increase in blood urea nitrogen of 5.9 mg/dl vs. 3.3 mg/dl, p < 0.001
- increase in serum creatinine of 0.18 mg/dl vs. 0.10 mg/dl, p < 0.001

3.3. Conclusion

A randomised double-blind study (Val-Heft) of 5010 patients with stable NYHA class II, III or IV heart failure has compared valsartan 160 mg 2× daily with placebo, in both cases in combination with optimal standard therapy (OST) for heart failure.

After an average follow-up period of 23 months, there was no difference in all-cause mortality between the valsartan/OST group (19.7%: 495/2511 patients) and the placebo/OST group (19.4% 484/2499 patients); RR 1.02 [0.90; 1.15].

The composite primary endpoint (all-cause mortality, resuscitated cardiac arrest, hospitalisation due to heart failure, IV administration of an inotropic or vasodilator drug for at least 4 hours without hospitalisation) was significantly reduced in the valsartan/OST group compared with the placebo/OST group (28.8% vs. 32.1%). RR 0.87 [0.79; 0.96].

This difference is mainly due to the reduction in hospitalisations for heart failure (13.9% vs. 18.5%), which account for 53% of the total events observed.

There is no available direct comparison with other sartans indicated in heart failure patients.

The most frequently observed adverse events (> 1%) were: dizziness, hypotension, renal impairment, asthenia, diarrhoea, and elevations in blood urea nitrogen, serum creatinine and potassium.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual clinical benefit

Symptomatic heart failure is a serious condition which, due to its complications, can be life-threatening.
These medicinal products are curative treatments.
The management of heart failure involves the use of several classes of drug, in particular diuretics, ACE inhibitors and beta-blockers. Valsartan has been shown to be of benefit when angiotensin-converting enzyme (ACE) inhibitors cannot be used or as add-on therapy to ACE inhibitors when beta-blockers cannot be used.
These medicinal products are second-line therapies.

> Public health benefit:
> Symptomatic heart failure is a common and serious pathological condition. In this extension of the indication, the population likely to benefit from this treatment represents a moderate public health burden.
> Improving the management of heart failure remains a public health need that is an established priority (Public Health Law 2004*).
> Based on the available data, valsartan is not expected to have any impact on morbidity/mortality compared with other therapies.
> Moreover, it is not certain whether these results can be carried over into clinical practice, in particular given the risk of hyperkalaemia.
> Consequently, it is not expected that the TAREG products will benefit public health in this extension of the indication.
> ** Public Health Law 2004: Law No. 2004-806 of 9 August 2004 on public health policy: objective in heart failure No. 73 [rapport_DREES_indicateurs - July 2005]*

The efficacy/adverse effects ratio of valsartan in this indication is high.
The actual benefit of TAREG in this indication is substantial.

4.2. Improvement in actual benefit (IAB)

TAREG provides no improvement in actual clinical benefit (IAB V) in the management of symptomatic heart failure when ACE inhibitors cannot be used or in combination with an ACE inhibitor when beta-blockers cannot be used.

4.3. Therapeutic use [2]

The management of heart failure patients with reduced systolic ventricular function (ejection fraction ≤ 40%) involves the combined prescription of a diuretic (thiazide or loop), an ACE inhibitor (or an angiotensin-II antagonist if unable to tolerate ACE inhibitors), and also a digitalis glycoside in the majority of cases. The prescription of a beta-blocker (bisoprolol, carvedilol, metoprolol or nevibolol) must be considered in patients with “stable” heart failure, as this achieves a further reduction in mortality.

In class III and IV heart failure according to the NYHA classification, the addition of low-dose spironolactone (25 to 50 mg/day) is indicated in patients with serum potassium < 5.5 mmol/l and serum creatinine < 220 µmol/l, as this reduces both mortality (total and cardiovascular) and the risk of hospitalisation due to worsening heart failure.

[2] Working group on the diagnosis and treatment of chronic heart failure, European Society of Cardiology. “Recommandations pour le diagnostic et le traitement de l’insuffisance cardiaque congestive” [Recommendations on the diagnosis and treatment of congestive heart failure]. Arch Mal Cœur Vaisseaux, 2006, 99 (Suppl 2)

In class II and III heart failure according to the NYHA classification with LVEF < 40%, angiotensin-II antagonists are an alternative to ACE inhibitors in patients unable to tolerate ACE inhibitors or in combination with an ACE inhibitor in patients who remain symptomatic under diuretic/ACE inhibitor/beta-blocker triple therapy. However, these combinations should be considered only after (re-)evaluation of their benefit/risk ratio. Moreover, the triple combination of valsartan/ACE inhibitor/aldosterone antagonist diuretic is highly inadvisable because of the risk of hyperkalaemia.
Like the other angiotensin-II antagonists indicated in NYHA class II and III heart failure with LVEF ≤ 40%, valsartan may be given in combination with other heart failure treatments (ACE inhibitors, beta-blockers, diuretics, digitalis glycosides) in patients unable to tolerate ACE inhibitors or who remain symptomatic under ACE inhibitors and in whom beta-blockers cannot be used.

4.4. Target population

In this indication, the target population of valsartan is patients with NYHA II and III heart failure and LVEF ≤ 40% who are unable to tolerate ACE inhibitors or who remain symptomatic under ACE inhibitors and in whom beta-blockers cannot be used.

The prevalence of heart failure in the general population is estimated at between 2 and 3%[3,4], i.e. between 1.2 and 1.8 million persons in France.
Approximately 50%[3,5] will have NYHA class II or III HF and an LVEF ≤ 40%, i.e. 600,000 to 900,000 persons.
a) Patients unable to tolerate ACE inhibitors
The proportion of patients unable to tolerate ACE inhibitors is estimated at between 5% and 10%[6,7], i.e. some 30,000 to 90,000 patients.
b) Patients symptomatic under ACE inhibitors and in whom beta-blockers cannot be used.
There are no available data on the proportion of patients remaining symptomatic under ACE inhibitors and in whom beta-blockers cannot be used.

The target population of valsartan in the treatment of symptomatic heart failure when ACE inhibitors cannot be used is estimated at between 30,000 and 90,000 patients.
The available epidemiological data do not allow us to accurately quantify the target population of valsartan in the treatment of symptomatic heart failure in combination with an ACE inhibitor when beta-blockers cannot be used.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the extension of the indication “Treatment of symptomatic heart failure when angiotensin-converting enzyme (ACE) inhibitors cannot be used or as add-on therapy to ACE inhibitors when beta-blockers cannot be used” and at the dosage in the marketing authorisation.

Packaging: Appropriate for the prescription conditions

Reimbursement rate: 65%

[3] Delahaye F, de Gevigney G. [Epidemiology of heart insufficiency]. Ann Cardiol Angeiol (Paris) 2001; 50(1): 6-11
[4] Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008; 29(19): 2388-2442.
[5] Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction. N Engl J Med 2006; 355: 251-9
[6] Bart BA. Contemporary management of patients with left ventricular systolic dysfunction: results from the study of patients intolerant of converting enzyme inhibitors (SPICE) registry. Eur Heart J 1999; 20: 1182-90
[7] Flather MD. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet. 2000 May 6; 355(9215): 1575-81