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 (mutual recognition):
TAREG 40 mg : 23/01/2006
TAREG 80 et 160 mg : 31/05/2001

Date of extension of the indication: 5 June 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 clinically stable patients with symptomatic heart failure (HF) or asymptomatic left-ventricular systolic dysfunction (LVSD) after recent (between 12 hours and 10 days) myocardial infarction”.

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.

After recent myocardial infarction
- Former indication: State after recent myocardial infarction (between 12 hours and 10 days) in clinically stable patients with asymptomatic left-ventricular systolic dysfunction and/or clinical or radiological signs of left-ventricular failure who are unable to tolerate angiotensin-converting enzyme (ACE) inhibitors.

- New indication: “Treatment of clinically stable patients with symptomatic heart failure (HF) or asymptomatic left-ventricular systolic dysfunction (LVSD) after 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 in combination with an ACE inhibitor when beta-blockers cannot be used.”

1.3. Dosage
“Recent myocardial infarction: In clinically stable patients, treatment may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, valsartan as add-on-therapy should be titrated to 40 mg, 80 mg and t160 mg twice daily over the next few weeks. The starting dose is provided by the 40 mg divisible tablet.
The target maximum dose is 160 mg twice daily. In general, it is recommended that patients achieve a dose level of 80 mg twice daily by two weeks after treatment initiation and that the target maximum dose, 160 mg twice daily, be achieved by three months, based on the patient’s tolerability. If symptomatic hypotension or renal dysfunction occur, consideration should be given to a dosage reduction.
Valsartan may be used in patients treated with other post-myocardial infarction therapies, for example thrombolytics, acetylsalicylic acid, beta-blockers, statins and diuretics. The combination with ACE inhibitors is not recommended.
Evaluation of post-myocardial infarction patients should always 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 of valsartan should not exceed 80 mg. TAREG is contraindicated in patients with severe hepatic impairment and in 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 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, plain
C09CA: Angiotensin II antagonists, plain
C09CA03: Valsartan

2.2. Medicines in the same therapeutic category:
There are no other angiotensin-II antagonists in a non-combined (plain) form indicated in the treatment of patients after a recent MI.

2.3. Medicines with a similar therapeutic aim
All other medicines indicated in the cardiovascular protection of patients after recent myocardial infarction.
3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy
The dossier is based on the VALIANT\textsuperscript{1} (Valsartan in Acute Myocardial Infarction) study, which has already been submitted and evaluated by the transparency Committee in March 2006.

- Summary of the methodology and results of the VALIANT study:

Objective: To evaluate the efficacy and safety of valsartan (n = 4909) compared with a valsartan+captopril combination (n = 4885) and with captopril alone (n = 4909) in patients with heart failure and/or left-ventricular systolic dysfunction after a recent myocardial infarction.

Method: Comparative, controlled, randomised, double-blind study carried out in 14,703 patients followed up for an average of 24 months. The initial analysis consisted of an analysis of the superiority of valsartan or of the valsartan+captopril combination compared with captopril. An analysis of non-inferiority between valsartan and captopril was specified in the protocol in the event that valsartan was not superior to captopril. Non-inferiority was demonstrated if the upper limit of the confidence interval of the difference was below a limit set at 1.13 for the hazard ratio.

Inclusion criteria: Patients with recent myocardial infarction (0.5 to 10 days before inclusion) who are clinically stable, with left-ventricular systolic dysfunction (ejection fraction $\leq 40\%$ to isotopic ventriculography or $\leq 35\%$ to echocardiography or to ventricular contrast angiography) and/or clinical or radiological signs of left-ventricular failure.

Exclusion criteria: Systolic arterial pressure $< 100$ mmHg and serum creatinine $> 221$ µmol/l.

NB: Inability to tolerate ACE inhibitors was an exclusion criterion in this study.

Treatment: Patients were randomised into three groups:
- valsartan (initial dose 20 mg twice daily up to the maximum dose of 160 mg twice daily), n = 4909
- captopril (initial dose 6.25 mg three times daily up to the maximum tolerated dose of 50 mg three times daily), n = 4909
- valsartan+captopril combination, n = 4885. In this latter group, the valsartan dose was titrated from 20 mg twice daily to 80 mg twice daily; the captopril dose was the same as in the monotherapy group.

Primary endpoint: All-cause mortality.
Two comparisons were specified for the primary endpoint: comparison between valsartan and captopril and comparison between the valsartan+captopril combination and captopril.

RESULTS: See Table 1
The main analysis was on an ITT basis. A PP analysis was carried out for non-inferiority.

On inclusion, the patients’ characteristics were comparable. The patients mostly belonged to classes I and II of the NYHA classification.
Among patients still undergoing the treatment after one year, the average daily dose was 247 mg in the valsartan group, 116 and 107 mg in the valsartan+captopril group and 117 mg in the captopril group.

\textsuperscript{1} Pfieffer et al. “Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both” N Engl J Med 2003; 349: 1893-906.
Concomitant treatments were: ASA (85% at 1 year), beta-blocker (71% at 1 year), ACE inhibitor (40% at inclusion, 7.3% at 1 year), other platelet-aggregation inhibitor and oral anticoagulants and statins. The study population was composed of 69% men, 94% Caucasians and 53% patients aged 65 years and over.

Table 1: Number and percentage of all-cause deaths observed after 24 months

<table>
<thead>
<tr>
<th></th>
<th>Valsartan (n = 4909)</th>
<th>Valsartan + captopril (n = 4885)</th>
<th>Captopril (n = 4909)</th>
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</thead>
<tbody>
<tr>
<td><strong>Intention-to-treat analysis</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>- Number of events [%]</td>
<td>979 (19.9%)</td>
<td>941 (19.3%)</td>
<td>958 (19.5%)</td>
</tr>
<tr>
<td>- Reduction in relative risk versus captopril [95% CI]</td>
<td>HR 1</td>
<td>HR 0.98</td>
<td>NS</td>
</tr>
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<td></td>
<td>95% CI [0.90; 1.11]</td>
<td>95% CI [0.89; 1.09]</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Per-protocol analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Number of events [%]</td>
<td>786 (16.5)</td>
<td>757 (15.9)</td>
<td>779 (16.3)</td>
</tr>
<tr>
<td>- Reduction in relative risk versus captopril [95% CI]</td>
<td>HR 0.98</td>
<td>HR 0.99</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>[0.87; 1.10]</td>
<td>[0.88; 1.12]</td>
<td>NS</td>
</tr>
</tbody>
</table>

After two years of treatment, mortality of all causes was observed in 979/4909 (19.9%) of patients treated with valsartan versus 958/4909 (19.5%) of patients treated with captopril, HR 1, 95% CI [0.90-1.11], NS (intention-to-treat analysis). This result does not demonstrate the superiority of valsartan or of the valsartan+captopril combination over captopril. In the per-protocol analysis, 786 deaths (16.5%) of all causes were observed in the valsartan group versus 779 (16.3%) in the captopril group, HR 0.98, 95% CI [0.87; 1.10], NS. The upper limit of the confidence interval was below the limit set at 1.13; the non-inferiority of the treatments was therefore demonstrated.

3.2. Adverse effects

In the VALIANT study, the percentage of definitive discontinuations of treatment on account of adverse events was 5.8% in the valsartan group and 7.7% in the captopril group; the principal causes were hypotension (1.4% vs. 0.8%) and renal impairment (1.1% vs. 0.8%).

A reduction in dosage due to adverse effects was documented in 29.4% of patients in the valsartan group and in 28.4% of patients in the captopril group; the principal causes were cough (0.6% vs. 2.5%), symptomatic hypotension (15.1% vs. 11.9%), hyperkalaemia (1.3% vs. 0.9%), renal impairment (4.9% vs. 3%, of which 3% vs. 1.9% of patients showed a serum creatinine elevation) and cough (1.7% vs. 5%).

The serious non-fatal adverse events reported with an incidence ≥ 0.1% and observed more frequently with valsartan than with captopril were arterial hypotension (29/4885 patients (0.6%) vs. 23/4879 patients (0.5%)) and acute renal failure (14/4885 (0.3%) vs. 6/4879 patients (0.1%)).

Laboratory findings: a doubling in serum creatinine was observed more often in the patients on valsartan (4.2%) than in those on captopril (3.4%).

According to the SPC, the adverse effects most commonly observed in patients with heart failure and/or left ventricular dysfunction after a recent myocardial infarction were dizziness, hypotension, orthostatic hypotension and renal impairment.
3.3. Conclusion

The efficacy and tolerance of valsartan in 14,703 patients with heart failure and/or left-ventricular systolic dysfunction after a recent myocardial infarction have been evaluated in a randomised, double-blind comparative study (VALIANT) of valsartan (initial dose 40 mg/day; maximum dose 320 mg/day) versus captopril (initial dose 18.75 mg/day; maximum dose 150 mg/day) versus a combination of valsartan (initial dose 40 mg/day; maximum dose 160 mg/day) and captopril (initial dose 18.75 mg/day; maximum dose 150 mg/day).

After an average follow-up period of two years, mortality of all causes was observed in 979/4909 (19.9%) of patients treated with valsartan alone versus 958/4909 (19.5%) of patients treated with captopril alone, HR 1, 95% CI [0.90-1.11], NS. This result does not demonstrate the superiority of valsartan alone or of the valsartan+captopril combination over captopril alone.

In the per-protocol analysis, 786 deaths (16.5%) of all causes were observed in the valsartan group versus 779 (16.3%) in the captopril group, HR 0.98, 95% CI [0.87; 1.10], NS. The upper limit of the confidence interval is below the limit set at 1.13; the non-inferiority of the treatments was demonstrated.

In this study, the serious adverse events observed more frequently with valsartan than with captopril were arterial hypotension (0.6% vs. 0.5%), acute renal failure (0.3% vs. 0.1%) and a doubling in serum creatinine (4.2% vs. 3.4%).

The non-inferiority of valsartan compared with captopril was demonstrated in the VALIANT study. In a mortality study, the reduced likelihood inherent in the non-inferiority hypothesis must be compensated by major tolerance benefits. However, such benefits were not observed, as major adverse effects (renal impairment, hypotension) were more common with valsartan than with captopril.

According to the SPC, the adverse effects most commonly observed in patients with heart failure and/or left ventricular dysfunction after a recent myocardial infarction were dizziness, hypotension, orthostatic hypotension and renal impairment.
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit
State after recent myocardial infarction in patients with left-ventricular systolic dysfunction is a serious condition which can be life-threatening.

Valsartan is a first-line treatment.

In patients who have recently suffered a myocardial infarction, valsartan is an element of the overall treatment strategy in combination with drugs of other therapeutic categories.

Public health benefit: State after myocardial infarction accompanied by left-ventricular systolic dysfunction 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. 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 indication.


The efficacy/adverse effects ratio for these medicinal products is high.

The actual benefit of TAREG in this extension of the indication is substantial.

4.2. Improvement in actual benefit (IAB)
TAREG provides no improvement in actual benefit (IAB V) in the management of clinically stable patients with symptomatic heart failure (HF) or asymptomatic left-ventricular systolic dysfunction (LVSD) after recent (between 12 hours and 10 days) myocardial infarction.

4.3. Therapeutic use

The occurrence of left-ventricular systolic dysfunction following a recent myocardial infarction worsens the prognosis. Its treatment is aimed at reducing cardiovascular morbidity/mortality.

Certain ACE inhibitors, certain beta-blockers and eplerenone are of proven efficacy in such situations. Spironolactone has proven effective in patients with chronic heart failure of all aetiologies taken together (RALES study).

The results of the VALIANT study show that valsartan can be used after a recent myocardial infarction in clinically stable patients with asymptomatic left-ventricular systolic dysfunction and/or clinical or radiological signs of left-ventricular failure.

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3 ACC/AHA 2007 “Guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction, 2007”
In clinically stable patients with symptomatic heart failure or asymptomatic left-ventricular systolic dysfunction, valsartan should be commenced between 12 hours and 10 days after myocardial infarction, provided renal impairment and serum potassium > 5.0 mmol/l are absent. Because valsartan is likely to cause hyperkalaemia, its use in combination with other treatments that increase potassium levels should be considered only after (re-)evaluation of the benefit/risk ratio. This risk of potentially life-threatening hyperkalaemia is higher in the elderly, in renal impairment and in diabetics.

4.4. Target population

In this extension of the indication, the target population of valsartan is represented by patients who have had a recent myocardial infarction and who have left-ventricular systolic dysfunction. It can be estimated from the following data:

- Based on the FAST-MI registry data (French registry of acute coronary syndromes with or without ST-segment elevation) extrapolated to the whole of France, the number of patients admitted each year to cardiological intensive-care units with a diagnosis of MI is estimated at 62,000 (32,000 patients with a diagnosis of MI ST+ and 30,000 with a diagnosis of MI ST-). In-hospital mortality was 5.8% for MI ST+ and 4.9% for MI ST-, which corresponds to approximately 3300 patients per year.

- The prevalence of left-sided heart failure and/or left-ventricular dysfunction (LVEF ≤ 40%) in the acute phase of MI is estimated at between 13 and 40%5.6.7.8.9.10, i.e. between 4000 and 13,000 patients per year.

The target population of valsartan in the treatment of clinically stable patients with symptomatic heart failure or asymptomatic left-ventricular systolic dysfunction after recent myocardial infarction can be estimated at between 4000 and 13,000 patients newly treated each year.

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 clinically stable patients with symptomatic heart failure (HF) or asymptomatic left-ventricular systolic dysfunction (LVSD) after recent (between 12 hours and 10 days) myocardial infarction” and at the dosage in the marketing authorisation.

Packaging: Appropriate for the prescription conditions

Reimbursement rate: 65%

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