HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

02 November 2005

ATACAND 4 mg, scored tablet
B/28; B/98
ATACAND 8 mg, scored tablet
B/28; B/98
ATACAND 16 mg, scored tablet
B/28; B/98
ATACAND 32 mg, scored tablet
B/28; B/98

Applicant : AstraZeneca Laboratories

candesartan cilexetil

List I

Date of Marketing Authorisation for this indication: Atacand 4, 8 and16 mg: 23 May 2005
Atacand 32 mg: 26 September 2005

Reason for application: Inclusion on the list of medicinal products reimbursed by National Insurance and approved for use by hospitals in the indication “Treatment of NYHA class II or III heart failure with left systolic ventricular dysfunction (LVEF ≤ 40%)”

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
candesartan cilexetil

1.2. Indications

ATACAND 4 mg, 8 mg, 16 mg
・Treatment of essential hypertension.
・Treatment of NYHA class II or III heart failure with left ventricular systolic dysfunction (LVEF ≤ 40%):
- if angiotensin-converting enzyme (ACE) inhibitors are not tolerated;
- or in combination with an ACE inhibitor in patients who remain symptomatic under ACE inhibitor therapy.

This indication is based on the results of the CHARM-Alternative and CHARM-Added trials.

ATACAND 32 mg
・Treatment of NYHA class II or III heart failure with left ventricular systolic dysfunction (LVEF ≤ 40%):
- if angiotensin-converting enzyme (ACE) inhibitors are not tolerated;
- or in combination with an ACE inhibitor in patients who remain symptomatic under ACE inhibitor therapy.

This indication is based on the results of the CHARM-Alternative and CHARM-Added trials.

1.3. Dosage

The starting dose usually recommended is 4 mg/day once daily. The dose is then gradually increased to the target dose of 32 mg/day or the highest tolerated dose, by doubling the dose at intervals of at least 2 weeks.
Any drug acting on the renin-angiotensin-aldosterone system may cause hyperkalaemia. This potentially fatal risk is higher in elderly patients, patients with renal failure, and diabetics. Candesartan may be given in combination with other drugs used to treat heart failure, such as ACE inhibitors, beta-blockers, diuretics, or digitalis; or with a combination of these drugs. However, co-prescription should not be considered until the risk/benefit ratio has been (re)assessed.
A triple combination of candesartan with an ACE inhibitor and a diuretic likely to induce hyperkalaemia (such as spironolactone or eplerenone) should be strictly avoided.
(see SPC).

2. SIMILAR MEDICINAL PRODUCTS

2.1. **ATC Classification (2004):**

C : Cardiovascular system
09 : Agents acting on the renin-angiotensin system
C : Angiotensin II antagonists
A : Angiotensin II antagonists, plain
06 : Candesartan

2.2. Medicines in the same therapeutic category
This is the first angiotensin II antagonist (sartan) for the management of heart failure.

2.3. Medicines with the same therapeutic aim
All medicinal products indicated in the management of heart failure, notably diuretics, digitalis, ACE inhibitors and beta-blockers.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy and safety data for candesartan in heart failure are based on the results of two phase III trials, CHARM-Alternative and CHARM-Added (Candesartan in Heart failure – Assessment of Reduction in Mortality and morbidity).

CHARM-Alternative

Objective: to compare the efficacy and safety of candesartan (n=1013) with placebo (n=1015) in patients with symptomatic heart failure, LVEF $\leq$ 40%, and ACE inhibitor intolerance.

Methodology:
- randomised double-blind placebo-controlled clinical trial.
- inclusion criteria: patients aged over 18 with stage II–IV heart failure and LVEF $\leq$ 40%, and ACE inhibitor intolerance.
- exclusion criteria: serum creatinine ≥ 265 µmol/L, serum potassium ≥ 5.5 mmol/L, systolic blood pressure > 170 mmHg, or diastolic blood pressure > 100 mmHg under treatment, history of myocardial infarction or recent stroke.
- primary endpoint: composite endpoint of cardiovascular death or admission to hospital for CHF.
- secondary endpoints: cardiovascular death, admission to hospital for CHF, all-cause death and a composite endpoint of all-cause death or admission to hospital for CHF.
- candesartan was initiated at a dose of 4 or 8 mg once daily, depending on the patient's haemodynamic status. The dose was then gradually increased in two-week stages depending on how well the drug was tolerated.
- the results were analysed by intent to treat after a mean follow-up of 34 months.

Results:
- patient characteristics at inclusion were: higher proportion of males (68%), average age 66, 47.6% in NYHA stage II and 48.8% in NYHA stage III. Half the patients had arterial hypertension and 27% had diabetes. These characteristics were similar for both groups.
- reasons for ACE inhibitor intolerance were cough (72%), hypotension (13%), renal dysfunction (12%) and angioedema/anaphylaxis (4%).
- the main drugs being used at inclusion were diuretics (85% of patients), beta-blockers (55%), digitalis (45%), spironolactone (24%) and calcium antagonists (16%).
- Six months into the trial, the average dose of candesartan was 23 mg/day. Fifty-nine percent (59%) of patients had reached the target dose of 32 mg/day (73% in the placebo group) and 30% had discontinued treatment (29% in the placebo group).
- the table below summarises the main results:

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	Placebo (n=1015)	Candesartan (n=1013)	Reduction in relative risk Reduction in absolute risk NNT	p
CV death or admission to hospital for CHF	406 (40%)	334 (32.9%)	23% 7.1% 14	S
All-cause death or admission to hospital for CHF	433 (42.6%)	371 (36.6%)	20% 6% 17	S
Admission to hospital for CHF	286 (28.1%)	207 (20.4%)	32% 7.7% 13	S
Cardiovascular death	252 (24.8%)	219 (21.6%)	15% 3.2%	NS
All-cause death	296 (29.1%)	265 (26.1%)	13% 3%	NS

After 34 months of treatment, the risk of cardiovascular death or admission to hospital for CHF was reduced by 23% in the candesartan group compared with the placebo group. There was a 7.1% reduction in absolute risk, and the number needed to treat to prevent these endpoints was 14.

CHARM-Added

Objective: to compare the efficacy and safety of candesartan (n=1 276) against placebo (n=1 272) in patients with symptomatic heart failure and LVEF $\leq$ 40%, and already treated with an ACE inhibitor.

Methodology:

- randomised double-blind placebo-controlled clinical trial
- inclusion criteria: patients aged over 18 with stage II–IV heart failure and LVEF $\leq$ 40%, and already treated with an ACE inhibitor.
- exclusion criteria: serum creatinine ≥ 265 µmol/L, serum potassium ≥ 5.5 mmol/L, systolic blood pressure > 170 mmHg, or diastolic blood pressure > 100 mmHg under treatment, history of myocardial infarction or recent stroke.
- primary endpoint: composite endpoint of cardiovascular death or admission to hospital for CHF.
- secondary endpoints: cardiovascular death, admission to hospital for CHF, all-cause death and a composite endpoint of all-cause death or admission to hospital for CHF.
- candesartan was initiated at a dose of 4 or 8 mg once daily, depending on the patient's haemodynamic status. The dose was then gradually increased in two-week stages depending on how well the drug was tolerated.
- the results were analysed by intent to treat after a mean follow-up of 41 months.

Results:

- patient characteristics at inclusion were: higher proportion of males (79%), average age 64, 24.1% in NYHA stage II and 72.8% in NYHA stage III. Half the patients had arterial hypertension and 30% had diabetes. These characteristics were similar for both groups.
- the main drugs used at inclusion, in addition to ACE inhibitors, were diuretics (90%), digitalis (58%), beta-blockers (55%) and spironolactone (17%).
- the ACE inhibitors used were enalapril (average dose 17 mg/day), lisinopril (17.5 mg/day), captopril (82 mg/day) or ramipril (7 mg/day).
- the table below summarises the main results:

	Placebo (n=1272)	Candesartan (n=1276)	Reduction in relative risk Reduction in absolute risk NNT	p
CV death or admission to hospital for CHF	538 (42.3%)	483 (37.8%)	15% 4.4% 23	S
All-cause death or admission to hospital for CHF	587 (46.1%)	539 (42.3%)	13% 3.9% 26	S
Admission to hospital for CHF	356 (28.9%)	309 (24.2%)	17% 3.8% 27	S
Cardiovascular death	347 (27.3%)	302 (23.7%)	16% 3.6% 28	S
All-cause death	412 (32.4%)	377 (29.5 %)	11% 2.8%	NS

After 41 months of treatment, the risk of cardiovascular death or admission to hospital for CHF was reduced by 15% in the candesartan group compared with the placebo group. There was a 4.4% reduction in absolute risk, and the number needed to treat to prevent these endpoints was 23.

Analysis of combined data from the CHARM-Alternative and CHARM-Added trials

The CHARM programme included an analysis of the combined data from both trials. This showed a statistically significant reduction in all-cause death, in cardiovascular death and in admissions to hospital for CHF.
The results of this combined analysis are shown in the table below:

	Placebo (n=2287)	Candesartan (n=2289)	Reduction in relative risk Reduction in absolute risk NNT	p
All-cause death	708 (31%)	642 (28%)	12% 2.9% 34	S
Cardiovascular death	599 (26.2%)	521 (22.8%)	16% 3.4% 29	S
Admission to hospital for CHF	642 (28.1%)	516 (22.5%)	24% 5.5% 18	S
All-cause death or admission to hospital for CHF	1020 (44.6%)	910 (39.8%)	16% 4.8% 21	S
CV death or admission to hospital for CHF	944 (41.3%)	817 (35.7%)	18% 5.6% 18	S

The beneficial effects of candesartan on cardiovascular death and admission to hospital for CHF were observed irrespective of age, sex or type of combined therapy.

3.2. Undesirable effects

The most common adverse events in both trials (≥1/100, <1/10) were:
- renal impairment: raised serum creatinine and/or urea levels,
- hyperkalaemia,
- hypotension.

These events were more common in patients over 70, diabetics, or those who had received other drugs acting on the renin-angiotensin-aldosterone system.

CHARM-Alternative trial:

21.7% of patients in the candesartan group (220/1013) discontinued treatment because of adverse events, compared with 19.4% in the placebo group (197/1015).

The main reasons for discontinuing treatment in the candesartan group and their frequency compared with the placebo group were:
- renal impairment: 6.4% vs. 2.5%
- hypotension: 4.5% vs. 1.4%
- hyperkalaemia: 2.1% vs. 0.3%

CHARM-Added trial:

24.3% of patients in the candesartan group (310/1276) discontinued treatment because of adverse events, compared with 17.6% in the placebo group (224/1272).

The main reasons for discontinuing treatment in the candesartan group and their frequency compared with the placebo group were:
- renal impairment: 8.2% vs. 4.2%
- hypotension: 5.4% vs. 3.5%
- hyperkalaemia: 3.8% vs. 0.9%

3.3. Conclusion

Two clinical trials comparing candesartan with placebo in a population with heart failure with left ventricular systolic dysfunction, ACE inhibitor intolerant or receiving combined treatment with ACE inhibitors, showed that adding candesartan to conventional treatment achieved a further reduction in morbidity and mortality. Global analysis of both trials showed a 12% reduction in relative risk of all-cause death and a 2.9% reduction in absolute risk after a mean of 3 years of treatment.

The most common undesirable effects were renal impairment, hyperkalaemia and hypotension. There was a substantial risk of hyperkalaemia, especially with a triple combination of candesartan, ACE inhibitor and a diuretic likely to cause hyperkalaemia.

4. CONCLUSIONS OF THE TRANSPARENCY COMMITTEE

4.1. Actual benefit

NYHA class II or III heart failure with left ventricular systolic dysfunction is a potentially life-threatening condition.

These drugs are curative therapy.

Management of heart failure relies on several classes of medication, particularly diuretics, ACE inhibitors, and beta-blockers. Candesartan has demonstrated benefit in patients with ACE inhibitor intolerance or in combination with ACE inhibitors in patients who remain symptomatic under ACE inhibitor therapy.

These drugs are second-line therapy.

Benefit to public health:
Heart failure is a common and serious condition. Since the population likely to benefit from this treatment under this new indication is fairly small, the contribution to public health may be regarded as moderate.
The requirements for heart failure therapy are still not adequately covered by existing therapies, especially among patients who are ACE inhibitor intolerant and those who remain symptomatic under ACE inhibitor therapy.
In view of the results of the CHARM trials, the anticipated impact on morbidity and mortality in the treated population is moderate. However, it is not certain that these results will be the same in clinical practice, especially as regards the risk of hyperkalaemia.
It is therefore expected that candesartan will benefit public health. This benefit is minor.

The efficacy/safety ratio for candesartan is high.

The actual benefit of candesartan in this indication is substantial.

4.2. Improvement in actual benefit

In patients with ACE inhibitor intolerance, candesartan has demonstrated a reduction in cardiovascular morbidity and mortality in patients with NYHA class II to III heart failure and left ventricular systolic dysfunction. Candesartan offers a substantial improvement in actual benefit (ASMR II) in the management of these patients.

In combination with an ACE inhibitor in patients who remain symptomatic under ACE inhibitor therapy, candesartan has demonstrated a reduction in cardiovascular morbidity and mortality in patients with NYHA class II to III heart failure and left ventricular systolic dysfunction. These patients have an increased risk of hyperkalaemia. Candesartan offers a moderate improvement in actual benefit (ASMR III) in the management of these patients.

4.3. Therapeutic use

Heart failure therapy aims to reduce symptoms and the risk of cardiovascular morbidity and mortality. Drugs such as ACE inhibitors, diuretics and beta-blockers have been shown to be effective in these situations.
Candesartan may be proposed for patients with NYHA class II to III heart failure and left ventricular systolic dysfunction when they are ACE inhibitor intolerant, or in combination with an ACE inhibitor in patients who remain symptomatic under ACE inhibitor therapy.
Candesartan may be given in combination with other drugs for heart failure such as ACE inhibitors, beta-blockers, diuretics, digitalis, or with a combination of these drugs.
However, co-prescription should not be considered until the risk/benefit ratio has been (re)assessed. A triple combination of candesartan with an ACE inhibitor and a diuretic likely to cause hyperkalaemia should be strictly avoided.

4.4. Target population

The target population for candesartan in this indication is patients with NYHA class II or III heart failure and LVEF $\leq$ 40%) who are ACE inhibitor intolerant or who remain symptomatic under ACE inhibitor therapy.
This population can be estimated from the following data:
a) ACE inhibitor intolerance
- The prevalence of heart failure is about 500 000–600 000 in France (GTNDO, 2003).
- Around 50% of these cases are thought to be NYHA class II or III with LVEF $\leq$ 40% (Béguin, 2004), i.e. 250 000–300 000 people.
- Within this population, the proportion of patients who are ACE inhibitor intolerant is thought to be 5%–10% (Bart, 1999 – Flather, 2000), i.e. 12 500–30 000 patients.

b) symptomatic under ACE inhibitor therapy.
- Between 60% and 80% of patients in NYHA class II to III are thought to be treated with ACE inhibitors, i.e. between 150 000 and 240 000 patients.
- No data are available on the proportion of patients remaining symptomatic under ACE inhibitor therapy. On the assumption that they represent half of all patients (expert opinion), this population can be estimated to be between 75 000 and 120 000 patients.

N.B. The triple combination of candesartan, ACE inhibitor and a diuretic likely to cause hyperkalaemia is highly inadvisable. Patients already taking an ACE inhibitor and spironolactone (around 20% in the CHARM-Added trial) should not be treated with candesartan.

The total target population for candesartan in this indication would therefore be 90 000–150 000 patients.

4.5. Transparency Committee recommendations

The Committee recommends inclusion on the list of medicinal products reimbursed by National Insurance and approved for use by hospitals and various public services.

The Transparency Committee calls for a study of patients treated with candesartan for heart failure. Its aim will be to describe, in real-life treatment situations:
- the conditions under which these medicinal products are used (profile of patients treated including their age, compliance with the indication in the Marketing Authorisation, previous and co-prescribed therapies, procedures for monitoring serum potassium, etc.),
- frequency of and reasons for discontinuing treatment
- patients' clinical outcome.

Packaging: appropriate for the conditions under which it is prescribed

Reimbursement rate: 65%