HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

29 November 2006

PROCORALAN 5 mg, film-coated tablet
B/56 (CIP 371 676-2)
B/100 (CIP 567 208-1)

PROCORALAN 7.5 mg, film-coated tablet
B/56 (CIP 371 679-1)
B/100 (CIP 567 209-8)

Applicant: SERVIER

Ivabradine

List I

Date of Marketing Authorisation (MA): 25 October 2005

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for use by hospitals

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Ivabradine

1.2. Indication

Symptomatic treatment of chronic stable angina in patients with normal sinus rhythm, who have contraindication or intolerance to beta-blockers.

1.3 Dosage

For the different therapeutic doses, ivabradine is available as film-coated tablets containing 5 mg and 7.5 mg. The usual recommended starting dose of ivabradine is 5 mg twice a day. After three to four weeks of treatment, the dosage may be increased to 7.5 mg twice a day depending on the therapeutic response. If, during treatment, the heart rate persistently decreases below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward including the possible dose of 2.5 mg twice a day (one half 5 mg tablet twice a day). Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist. Tablets must be taken orally twice daily, i.e. once in the morning and once in the evening during meals.

Use in the elderly:
Since ivabradine has been studied in a limited number of patients aged 75 years or more, a lower starting dose should be considered for them (2.5 mg twice a day i.e. one half 5 mg tablet twice a day) before up-titration if necessary.
(Cf. SPC)

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006):

C : Cardiovascular system
01 : Medicinal products in cardiology
E : Other cardiology medicinal products
B : Other cardiology medicinal products
17 : Ivabradine

2.2. Medicines in the same therapeutic category
Ivabradine is the first medicinal product in this therapeutic class.

2.3. Medicines with a similar therapeutic aim

Patients with stable angina and a contraindication or intolerance to beta-blockers may be proposed calcium antagonists and in particular heart rate-decreasing agents (diltiazem, verapamil).

Other medicinal products: nitrates derivatives, nicorandil.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The anti-anginal and anti-ischaemic efficacy of ivabradine was analyzed in four randomised double-blind studies (two versus placebo, one versus atenolol and one versus amlodipine). These studies had common characteristics in terms of:

- Inclusion criteria: Men and women aged from 18 to 75 years with stable exercise induced angina for at least 3 months.
- Non inclusion criteria: Unstable or Prinzmetal angina, recent myocardial infarction or aortocoronary bypass surgery, stage III or IV heart failure, arterial hypotension or uncontrolled hypertension, hepatic (ALAT> 3 X N) or renal disorder (creatinine > 180 micromol/L), anaemia (Hb < 10 g/dl)...
- Efficacy evaluated using an exercise tolerance test (ETT) on a bicycle or treadmill.
- Endpoints: total exercise duration (TED), time to onset of 1 mm ST-segment depression (TST), time to appearance of limiting angina (TLA) and time to onset of angina pain (TOA); heart rate
- The baseline characteristics of enrolled patients were as follows: average age: approximately 60 years; proportion of men: approximately 85%; prior treatment by beta-blockers: approximately 60% of patients (beta-blockers were stopped during the run-in period before the studies)
- The study duration ranged from 2 weeks to 4 months.

Efficacy at one year was studied as a secondary endpoint in three other open-label safety studies, not described in this opinion. According to EMEA, these studies showed that the heart rate remained low and that there was a reduction in attacks of angina in these patients.

a. Study versus placebo (CL2-009) [1]

Objective: To compare the anti-anginal efficacy and safety of 3 doses of ivabradine [2.5 mg x 2/day (n=64); 5 mg x 2/day (n=59); 10 mg x 2/day (n=66)] with those of placebo (n=68), in patients with stable angina.

Design:

- Double-blind, randomised, placebo-controlled phase II study.
- Endpoints: TST (idem), TLA, TOA, as defined above, before and after two weeks of treatment. A comparison of the two groups was also performed (significant differences are shown in bold type)

1 Borer J.S. et al. Antianginal and antiischemic effects of ivabradine, an If inhibitor, in stable angina. Circulation. 2003; 107:817-823

Results:

Endpoint	Treatment groups	N	Difference relative to baseline (seconds)	Difference relative to placebo and 95% CI
TST	Placebo	68	9.0	
	Iva : 2.5 mg bid	64	32.0	23.0 [-7.6; 53.5]
	Iva : 5 mg bid	59	44.1	35.2 [4.0; 66.3]
	Iva : 10 mg bid	66	46.2	37.2 [6.9;67.5]
TLA	Placebo	68	12.7	
	Iva : 2.5 mg bid	64	22.5	9.8 [-14.4; 33.9]
	Iva : 5 mg bid	59	27.2	14.5 [-10.1; 39.2]
	Iva : 10 mg bid	66	40.8	28.1 [4.1; 52.0]
TAO	Placebo	68	24.7	
	Iva : 2.5 mg bid	64	37.6	13.0 [-15.8; 41.8]
	Iva : 5 mg bid	59	38.8	14.2 [-15.3; 43.6]
	Iva : 10 mg bid	66	69.4	44.7 [16.1; 73.3]

- Iva : Ivabradine

In this short-term study, ivabradine induced a reduction in heart rate and showed an anti-ischaemic and anti-anginal efficacy at doses of 5 mg bid and in particular, 10 mg bid, compared to placebo. The 3-month open-label follow-up study showed the maintenance of efficacy, the good safety of the drug and the lack of a rebound effect after sudden withdrawal.

b. Study versus atenolol (CL3-017)[2]

Objective: compare the anti-anginal efficacy and safety of ivabradine 7.5 mg bid (n=300) and 10 mg bid (n=298) with those of atenolol (n=286), in patients with stable angina.

Design:

- Randomised, double-blind, non-inferiority study versus atenolol. Non-inferiority was accepted if the lower limit of the confidence interval of the difference was greater than -35 seconds.
- Two periods: during the first period (1 month), the patients received reduced dosages of ivabradine and atenolol. Up-titration to the dosages described above was then carried out and maintained for 3 months.
- Primary efficacy endpoint: Measurement of TED after 4 months of treatment.

Results:

Endpoint	Treatment groups	N	Difference relative to baseline (seconds)	Difference relative to atenolol and 95% CI
TED	Iva: 7.5 mg bid	300	86.8	10.2 [-8.28 ; 28.8]
	Iva: 10 mg bid	298	91.7	15.7 [-2.9 ; 34.25]
	Ate:100 mg qd	286	78.8	
TLA	Iva: 7.5 mg bid	300	91.8	9.3 [-9.6 ; 28.3]
	Iva: 10 mg bid	298	96.9	15.0 [-3.9; 34.0]
	Ate:100 mg qd	286	85.4	
TAO	Iva: 7.5 mg bid	300	145.2	12.1 [-10.5; 34.7]
	Iva: 10 mg bid	298	139.6	10.1 [-12.5; 32.8]
	Ate:100 mg qd	286	135.2	
TST	Iva: 7.5 mg bid	300	98.0	4.3 [-16.8 ; 25.3]
	Iva: 10 mg bid	298	86.9	-3.3 [-24.4 ; 17.78
	Ate:100 mg qd	286	95.6	
Resting heart rate (bpm)	Iva: 7.5 mg bid	300	-14.3 bpm	2.1 [0.6 ; 3.7]
	Iva: 10 mg bid	298	-14.3 bpm	1.1 [-0.4 ; 2.7]
	Ate:100 mg qd	286	-15.6 bpm	

- Iva : Ivabradine
- Ate : Atenolo

2 Tardif J-C et al. Efficacy of ivabradine, a new selective If inhibitor, compared with atenolol in patients with chronic stable angina. European Heart Journal (2005) 26. 2529-2536

This 4-month study showed the non-inferiority of ivabradine 7.5 and 10 mg x bid compared to atenolol 100 mg/day on the above-described ergometric endpoints. No statistically significant difference was demonstrated between the two dosages of ivabradine.

c. Study versus amlodipine (CL3-023)

Objective: To compare the anti-anginal efficacy and safety of ivabradine 7.5 mg bid (n=381) and 10 mg bid (n=376) with those of amlodipine (n=398), in patients with stable angina.

Design:
- This study was a 3-months, randomised, double-blind, non-inferiority study. Non-inferiority was accepted if the lower limit of the confidence interval of the difference was greater than - 30 seconds.
- Primary efficacy endpoint: measurement of TED at trough of treatment compared to amlodipine at trough of drug activity after 3 months of treatment.

Results:

Endpoint	Treatment groups	N	Difference relative to baseline (seconds)	Difference relative to atenolol and 95% CI
TED	Iva: 7.5 mg bid Iva: 10 mg bid Amlo:10 mg qd	381 376 398	27.6 21.7 31.2	-1.8 [-14.6 ; 11.0] -6.6 [-19.5 ; 6.3]
TLA	Iva: 7.5 mg bid Iva: 10 mg bid Amlo:10 mg qd	381 376 398	29.9 22.9 32.7	-1.2 [-14.1 ; 11.7] -6.9 [-19.9; 6.0]
TAO	Iva: 7.5 mg bid Iva: 10 mg bid Amlo:10 mg qd	381 376 398	64.7 59.7 66.6	-0.6 [-15.2; 14.0] -4.6 [-19.2; 10.0]

- Iva : Ivabradine
- Amlo : Amlodipine

This 3-months study showed the non-inferiority of ivabradine 7.5 and 10 mg bid compared to amlodipine 10 mg/day for the above-described ergometric endpoints. According to the European Medicinal agency (EMEA) the results of this study may be criticised in terms of robustness, mainly as the non-inferiority limit of 30 seconds, was considered too wide.

d. Study versus placebo in combination with amlodipine (CL3-018)

Objective: to compare the anti-anginal efficacy and safety of ivabradine 5 mg bid (n=222) and 7.5 mg bid (n=229) versus placebo (n=277), in patients with symptomatic stable angina already treated by amlodipine 10 mg/day.

Design:
- This study was a 3-month, randomised, double-blind phase III study.
- Primary efficacy endpoint: (TED at trough of treatment) of the ivabradine + amlodipine combination compared to the placebo + amlodipine combination.

Results:

Endpoint	Treatment groups	N	Difference relative to baseline (seconds)	Difference relative to placebo and 95% CI
TED	Placebo	222	52.5	
	Iva : 5 mg bid	229	62.4	23.0 [-7.6; 53.5]
	Iva : 7.5 mg bid	277	58.3	35.2 [4.0; 66.3]
TST	Placebo	222	74.9	
	Iva : 5 mg bid	229	84.5	9.8 [-14.4; 33.9]
	Iva : 7.5 mg bid	277	81.6	14.5 [-10.1; 39.2]
TAO	Placebo	222	89.9	
	Iva : 5 mg bid	229	105.2	13.0 [-15.8; 41.8]
	Iva : 7.5 mg bid	277	104.9	14.2 [-15.3; 43.6]

- Iva : Ivabradine

This study did not demonstrate a significant difference between the two groups of patients at the trough of activity of the drug (primary efficacy endpoint), whereas an additional efficacy was observed at the peak (secondary endpoint). Hence, addition of ivabradine did not seem to provide a gain in efficacy for patients already treated by amlodipine alone.

3.2. Adverse effects

Procoralan was studied in nearly 2,900 patients during phase II and III clinical trials (the four studies described above and three other studies with safety analysis as their primary objective).

The most frequently observed adverse effects with ivabradine were dose-dependent and were related to the pharmacological effect of the drug.

According to the EMEA, the available studies demonstrated more adverse effects with ivabradine than with atenolol but as many adverse effects as with amlodipine.

The following adverse effects were reported during clinical trials:

- Visual luminous phenomena (phosphenes): reported by 14.5% of patients, described as a transient, mild to moderate, enhanced brightness in a limited area of the visual field and usually triggered by sudden changes in light intensity. They disappeared most of the time during treatment (77.5 % of cases) or after its discontinuation. Less than 1% of patients changed their a day routine or discontinued treatment because of phosphenes.
- Cardiovascular disorders: bradycardia: 3.3 % of patients, in particular during the first 2 or 3 months of treatment. 0.5% of patients presented severe bradycardia with a heart rate of 40 bpm or less; 1st degree atrioventricular block (1° AVB) ; ventricul ar extrasystoles
- General disorders: headaches, generally during the first month of treatment; dizziness, probably related to the bradycardia.

3.3. Conclusion

The efficacy and safety of ivabradine were evaluated in four comparative studies (two versus placebo, one versus atenolol and one versus amlodipine) and in three non-comparative studies with safety as primary objective.

Compared to placebo, ivabradine induced a reduction in heart rate and demonstrated an anti-ischaemic and anti-anginal efficacy on ergometric endpoints. Open-label follow-up showed the maintenance of this efficacy, good tolerability and the lack of a rebound effect after sudden drug withdrawal.

Compared to atenolol 100 mg/day, ivabradine 7.5 and 10 mg bid was shown to be non-inferior for ergometric efficacy variables. No statistically significant difference was demonstrated between the two dosages of ivabradine. According to the EMEA the available studies demonstrated more adverse effects with ivabradine than with atenolol.

Compared to amlodipine 10 mg/day, ivabradine 7.5 and 10 mg bid was shown to be non-inferior for the ergometric endpoints with no difference in the incidence of adverse effects.
In patients already taking amlodipine, a study showed that there was no significant difference between two groups of patients after addition of a placebo or ivabradine.

There is no study available versus other calcium inhibitors (especially diltiazem and verapamil). No study specifically enrolled patients with contraindications or intolerance to beta-blockers.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual Benefit

Stable chronic angina is generally the clinical sign of ischaemic heart disease. It is a frequent and serious disorder that may be life-threatening.

The efficacy/safety ratio of PROCORALAN, as determined in the available studies, is high.

PROCORALAN provides symptomatic treatment with the objective of improving symptoms and preventing recurrences of angina attacks.

PROCORALAN is a second-line treatment, for use in the case of a contraindication or intolerance to beta-blockers.
There are alternative medications: these are calcium antagonists and in particular heart-rate decreasing agents. A therapeutic need exists in patients with asymptomatic left ventricular dysfunction contraindicating the use of these drugs.

Public Health benefit:

Stable chronic angina is a frequent and serious pathological condition. As the population that may benefit from PROCORALAN treatment is limited to patients with a contraindication or intolerance to beta-blockers who are unable to receive treatment by rate-limiting calcium antagonists, the public health burden may be considered to be low.

The improvement in management of ischaemic heart disease is a public health requirement (GTNDO priority[3]), but the contribution of PROCORALAN in the limited population of angina patients with asymptomatic left ventricular dysfunction who are unable to be treated by heart rate-decreasing calcium antagonists, cannot be considered to be a public health priority.

Taking into account the results of available studies on intermediate endpoints (ergometric), an impact is expected on pain and quality of life. However it is not certain that these results may be transposed to clinical practice in particular because patients treated in clinical practice probably have a different profile than study patients.

Consequently, this proprietary drug is not expected to have an impact on public health.

The actual medical benefit of this proprietary drug in this indication is significant.

3 GTNDO: Groupe Technique National de Définition des Objectifs (DGS-2003)

4.2. Improvement in actual benefit:

The Transparency Committee considers that PROCORALAN provides a moderate improvement in actual benefit (IAB III) in patients with chronic stable angina with a contraindication or intolerance to beta-blockers and with asymptomatic left ventricular dysfunction (LVEF < 45%) contraindicating the use of heart rate-decreasing calcium antagonists.

4.3. Therapeutic use

According to the guidelines of European Society of Cardiology[4], in addition to secondary prevention measures (lifestyle and dietary rules, aspirin, statins) indicated in coronary artery disease, symptomatic treatment for stable angina may be prescribed to improve symptoms and prevent the recurrence of angina attacks.

First-line treatment involves the use of beta-blockers which reduce myocardial oxygen requirements by a combination of negative ionotropic, negative chronotropic bradycardia-inducing effects,, a slight reduction in systolic blood pressure, and revascularization by angioplasty and/or aortocoronary bypass surgery in patients who do not respond sufficiently to medication.

Heart rate-decreasing (verapamil, diltiazem) or non-heart rate decreasing (amlodipine etc.) calcium antagonists, long-acting nitrates and nicorandil may be used alone or in combination with beta-blockers, in particular for second-line therapy in the case of contraindications or intolerance to beta-blockers.

Ivabradine may be used as second-line treatment in patients with a normal sinus rythm, who have a contraindication or are intolerant to beta-blockers or a contraindication to calcium antagonists.
It is not recommended to combine ivabradine with heart rate decreasing calcium antagonists or beta-blockers.

4.4. Target population

The target population of ivabradine is represented by patients with chronic stable angina who have a contraindication or intolerance to beta-blockers. It may be estimated from the following data:

- A prevalence of stable angina of approximately 2% to 2.5% in the general population (Datamonitor Base, 2002; Montaye, 2006; ESC, 2006), i.e. approximately 1.3 to 1.5 million people in France;
- Approximately 10% to 20% of these patients (Crussade register 2005; Lindenauer, 2005; Daly, 2005) have a contraindication or intolerance to beta-blockers.

On these bases, the target population of PROCORALAN is approximately 130,000 to 300,000 patients.

Approximately 20 % of these patients (expert opinion) have asymptomatic left ventricular dysfunction contraindicating the use of heart rate-decreasing calcium antagonists, i.e. a population of 26,000 to 60,000 patients.

4.5. Transparency Committee Recommendations

The Committee recommends inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals and various public services in the Marketing Authorisation

4 Guidelines on the management of stable angina pectoris. European Society of Cardiology, 2006.

The Commission would like to be informed about the results of on-going studies and in particular those of the BEAUTIFUL study as soon as they are available.

4.5.1 Packaging: Appropriate for the prescription conditions

4.5.2 Reimbursement rate: 65%