



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

**TRANSPARENCY COMMITTEE**

OPINION

19 September 2012

**PROCORALAN 5 mg film-coated tablets**

**B/56 (CIP code: 371 676-2)**

**B/100 (CIP code: 567 208-1)**

**PROCORALAN 7.5 mg film-coated tablets**

**B/56 (CIP code: 371 679-1)**

**B/100 (CIP code: 567 209-8)**

**Applicant: SERVIER**

Ivabradine

ATC code: C01EB17 (other cardiac preparations)

List I

Date of Marketing Authorisation (centralised): 25 October 2005

Date of extension of indication to patients with heart failure: 9 February 2012

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance (B/56 only) and approved for hospital use (B/56 and B/100) in the extension of indication: "Treatment of chronic heart failure: Ivabradine is indicated in the treatment of chronic heart failure, NYHA class II to IV with systolic dysfunction, in patients in sinus rhythm and whose heart rate is  $\geq 75$  bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated".

Medical, Economic and Public Health Assessment Division

## 1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

### 1.1. Active ingredient

Ivabradine

### 1.2. Indications

#### Treatment of coronary artery disease:

Symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with with normal sinus rhythm. Ivabradine is indicated:

- in adults unable to tolerate or with a contraindication to the use of beta-blockers;
- or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and whose heart rate is > 60 bpm.”

#### Treatment of heart failure: new indication

**“Ivabradine is indicated in chronic heart failure, NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is  $\geq$  75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated (see Pharmacodynamics, section 5.1 of the SPC).”**

### 1.3. Dosage

“For the different therapeutic doses, film-coated tablets containing 5 mg and 7.5 mg ivabradine are available.

#### Treatment of chronic heart failure:

The treatment has to be initiated only in patients with stable heart failure. It is recommended that the treating physician should be experienced in the management of chronic heart failure. The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment, the dose can be increased to 7.5 mg twice daily if resting heart rate is persistently above 60 bpm, or decreased to 2.5 mg twice daily (one half 5 mg tablet twice daily) if resting heart rate is persistently below 50 bpm or in case of symptoms related to bradycardia such as dizziness, fatigue or hypotension. If heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.

If during treatment, heart rate decreases persistently below 50 bpm at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward to the next lower dose in patients receiving 7.5 mg twice daily or 5 mg twice daily.

If heart rate increases persistently above 60 bpm at rest, the dose can be up titrated to the next upper dose in patients receiving 2.5 mg twice daily or 5 mg twice daily.

Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist (see section 4.4 of the SPC).

#### Special populations:

*Elderly patients:* In patients aged 75 years or more, a lower starting dose should be considered in these patients (2.5 mg twice daily i.e. one half 5 mg tablet twice daily) before up-titration if necessary.

*Patients with renal impairment:* No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 ml/min (see section 5.2 of the SPC). No data are available in patients with creatinine clearance below 15 ml/min. Ivabradine should therefore be used with precaution in this population.

*Patients with hepatic impairment:* No dose adjustment is required in patients with mild hepatic impairment. Caution should be exercised when using ivabradine in patients with moderate hepatic impairment. Ivabradine is contra-indicated for use in patients with severe

hepatic insufficiency, since it has not been studied in this population and a large increase in systemic exposure is anticipated (see sections 4.3 and 5.2 of the SPC).

*Paediatric population:* The safety and efficacy of ivabradine in children aged below 18 years have not yet been established. No data are available.

**Method of administration:** Tablets must be taken orally twice daily, i.e. once in the morning and once in the evening during meals (see section 5.2 of the SPC)."

## 2. SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification (2012)

C	: Cardiovascular system
C01	: Cardiac therapy
C01E	: Other cardiac preparations
C01EB	: Other cardiac preparations
C01EB17	: Ivabradine

### 2.2. Medicines in the same therapeutic category

PROCORALAN is the only member of this therapeutic category.

### 2.3. Medicines with a similar therapeutic aim

All other drugs indicated in combination with standard treatments in the management of stable chronic heart failure associated with ventricular dysfunction:

- Potassium-sparing diuretics or aldosterone antagonists:
  - Eplerenone: INSPRA, indicated "in addition to standard therapy including beta-blockers in stable patients with LVEF  $\leq$  40% and clinical evidence of heart failure after recent myocardial infarction". **2005: substantial actual benefit; IAB III (incremental actual benefit) in patients with heart failure after recent myocardial infarction.**
  - Spironolactone: ALDACTONE and generics, indicated in the "treatment of stage III or IV heart failure (LVEF  $\leq$  35%), in combination with treatment including a loop diuretic, an ACE inhibitor, and a cardiac glycoside in the majority of cases". **2002: substantial actual benefit; IAB I.**

And all standard treatments for heart failure:

- Angiotensin-converting enzyme (ACE) inhibitors: first-line standard therapy: captopril (LOPRIL), cilazapril (JUSTOR), enalapril (RENITEC and generics), fosinopril (FOZITEC), lisinopril (PRINIVIL, ZESTRIL and generics), perindopril (COVERSYL and generics), ramipril (TRIA TEC).
- Angiotensin II receptor blockers (ARBs), in cases of intolerance to ACE inhibitors: candesartan (ATACAND, KENZEN) and valsartan (TAREG, NISIS and generics).
- Beta-blockers, indicated in stable heart failure: bisoprolol (CARDENSI EL, CARDI OCOR), carvedilol (KREDEX), metoprolol (SELOZOK), nebivolol (NEBILOX, TEMERIT).

### 3. ANALYSIS OF AVAILABLE DATA

The evaluation of the efficacy and safety of ivabradine in its extension of indication “*Ivabradine is indicated in chronic heart failure, NYHA class II to IV with systolic dysfunction, in patients in sinus rhythm and whose heart rate is  $\geq 75$  bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated*” is based on the SHIFT study (a pivotal study), the aim of which was to demonstrate the superiority of ivabradine compared to placebo on a composite morbidity-mortality endpoint in patients with stable heart failure on conventional therapy.

The pharmaceutical company also cited two ancillary studies to the SHIFT study:

- study NP30294 (Tardif et al. 2011<sup>1</sup>), the aim of which was to demonstrate the superiority of ivabradine on ventricular function (volume, ejection fraction), which, taking into account its methodology (subgroup of 411/6505 patients defined *a posteriori*), will not be discussed in this opinion;
- study NP30324 (Ekman et al. 2011<sup>2</sup>), the aim of which was to evaluate change in quality of life in a subgroup of patients from the SHIFT study (1944/6505 patients).

#### 3.1. Efficacy

##### 3.1.1. SHIFT study

Method: randomised, double-blind study comparing ivabradine, in combination with optimal treatment, to placebo in 6505 patients with stable heart failure, heart rate  $\geq 70$  bpm and LVEF  $\leq 35\%$ .

The duration of the study was dependent on the number of events observed; the study was stopped after 1600 observed events. The median duration of follow-up was 22.9 months.

Inclusion criteria: adult patients with heart failure of NYHA class II to IV, stable for at least four weeks on optimal treatment, and with:

- a documented prior history of hospitalisation for worsening heart failure within the 12 months preceding inclusion;
- sinus rhythm and resting heart rate  $\geq 70$  bpm;
- LVEF  $\leq 35\%$ .

Treatments:

- PROCORALAN, n = 3241
- Placebo, n = 3264

*PROCORALAN was administered at an initial dose of 5 mg twice daily. After 14 days of treatment, this dosage could be adjusted according to patients' heart rate and tolerance of the drug (2.5, 5 or 7.5 mg twice daily).*

Primary endpoint: composite endpoint combining the first of two events: cardiovascular death (including deaths of unknown origin) or hospitalisation for worsening heart failure.

Secondary endpoints included: each of the components of the composite primary endpoint.

Efficacy was also evaluated in eight subgroups of patients, formed *a priori*, including a subgroup defined by heart rate  $\geq 77$  bpm or  $< 77$  bpm and a subgroup defined by whether or not beta-blockers were taken on randomisation.

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1 Tardif JC et al; SHIFT Investigators. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography sub-study. Eur Heart J 2011; 32: 2507–2515.

2 Ekman I et al. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study. Eur Heart J 2011; 32: 2395–2404.

## RESULTS: intention to treat (see Table 1)

The characteristics of patients on inclusion were comparable.

Of the patients included, 1.2% had not been hospitalised for worsening heart failure in the 12 months preceding inclusion (inclusion criterion not met).

Concomitant treatments were distributed as follows:

- beta-blockers: 89.4% of patients in the ivabradine group versus 89.6% in the placebo group;
- ACE inhibitors and/or ARBs: 91.4% versus 90.7% (ACE inhibitors: 79.1% versus 78.2% and ARBs: 14% versus 14.5%);
- diuretics (excluding aldosterone antagonists): 83.9% versus 82.6%;
- aldosterone antagonists: 61.1% versus 59.5%;
- cardiac glycosides: 21.8% versus 21.8%.

The severity of heart failure was distributed as follows:

- two patients with class I heart failure: 0.03%
- 3169 patients with class II heart failure: 48.7%
- 3223 patients with class III heart failure: 49.5%
- 111 patients with class IV heart failure: 1.7%.

Only 26.1% of patients were treated with the doses of beta-blockers defined in European guidelines; 44.3% of patients received less than half the recommended dose.<sup>3</sup>

Table 1: first cardiovascular deaths (including deaths of unknown origin) or hospitalisations for worsening heart failure (composite primary endpoint).

	<b>PROCORALAN</b> n = 3241	Placebo n = 3264	Hazard ratio [95% CI] p
<b>Composite primary endpoint (CV deaths – hospitalisations for HF)</b>			
Number of events (%)	<b>793 (24.5%)</b>	937 (28.7%)	0.82 [0.75; 0.90], p < 0.0001
Secondary endpoints: - CV deaths - Hospitalisations for HF	449 (13.9%) 514 (15.9%)	491 (15%) 672 (20.6%)	0.91 [0.80; 1.03] NS 0.74 [0.66; 0.83] p < 0.0001

In this study, a significant reduction in the composite primary endpoint, combining cardiovascular deaths (including deaths of unknown origin) or the first hospitalisation for worsening heart failure, was observed in the ivabradine group in comparison to placebo: 793 events (24.5%) in the ivabradine group versus 937 events (28.7%) in the placebo group: HR = 0.82 [0.75; 0.90], p < 0.0001.

This result is mainly due to a reduction in first hospitalisations for worsening heart failure: 514 events (15.9%) versus 672 (20.6%), HR = 0.74 [0.66; 0.83], p < 0.0001. No significant difference was observed in terms of cardiovascular deaths between the two treatment groups.

In the subgroups of patients determined *a priori* according to heart rate  $\geq$  or  $<$  77 bpm, a significant reduction in the composite primary endpoint, combining cardiovascular deaths

<sup>3</sup> According to the study report, the most common reasons for not prescribing a beta-blocker were chronic obstructive pulmonary disease (34.5% of patients) and hypotension (18.6% of patients). The most common reasons for non-titration of beta-blockers to the maximum recommended dosage were hypotension (in 44.6% of patients who were not on the maximum recommended dose) or fatigue (31.9%).

(including deaths of unknown origin) or the first hospitalisation for worsening heart failure, was only observed in patients with a heart rate  $\geq 77$  bpm: HR = 0.75 [0.67; 0.85],  $p < 0.0001$ ; in these patients a significant reduction in cardiovascular mortality was also observed: HR = 0.81 [0.69; 0.96],  $p = 0.0137$ . In contrast, no significant difference was observed in patients with a heart rate  $< 77$  bpm.

For information, in patients with a heart rate  $\geq 77$  bpm, a subgroup was defined *a posteriori* according to whether or not ivabradine was combined with a beta-blocker. A significant reduction in the primary endpoint was observed in both groups (treated or not with beta-blockers). Although a significant reduction in hospitalisations for worsening heart failure was observed in patients treated or not with beta-blockers, a significant reduction in cardiovascular mortality was only observed in the group of patients not treated with beta-blockers: HR 0.50 [0.34; 0.76].

In the subgroup of patients determined *a priori* according to whether or not beta-blockers were taken, a significant reduction in the composite primary endpoint, combining cardiovascular deaths (including deaths of unknown origin) or the first hospitalisation for worsening heart failure, was observed in both predefined groups: patients treated with beta-blockers: 0.85 [0.76; 0.94], and patients not treated with beta-blockers: 0.68 [0.52; 0.88]. In these patients, although a significant reduction in first hospitalisations for worsening heart failure was observed in both groups, a significant reduction in cardiovascular mortality was only observed in the group of patients not treated with beta-blockers: HR 0.72 [0.52; 1.00].

### 3.1.2. Study NP30324

This quality of life study was conducted in a subgroup of patients from the SHIFT study, formed *a posteriori*; a total of 1944/6505 patients were included in this study.

The questionnaire used (KCCQ: Kansas City Cardiomyopathy Questionnaire) is a self-administered questionnaire comprising 23 questions<sup>4</sup> that can be used to generate two scores.<sup>5</sup> These two scores are the Overall Summary Score (OSS)<sup>6</sup> and the Clinical Summary Score (CSS).<sup>7</sup>

The “quality of life” data results from a comparison between ivabradine and placebo in terms of improvement in these two scores (OSS and CSS) between the start of the study and the end of the 12-month follow-up period:

- the overall OSS score improved by 7 points in the ivabradine arm versus 4 points in the placebo arm, with a difference of 2.4 points (95% CI = [0.9; 3.9],  $p < 0.001$ );
- the clinical CSS score improved by 5 points (on a scale of 0 to 100) in the ivabradine arm versus 3 points in the placebo arm, with an inter-group difference of 1.8 points (95% CI = [0.3; 3.2],  $p = 0.018$ ).

During the study, the OSS and CSS scores from the KCCQ had improved in both groups (ivabradine and placebo) with a statistically more significant improvement in the ivabradine arm. However, the difference in improvement of these scores between the ivabradine and placebo arms is very small (2 points on scales out of 100) and the confidence interval for this difference is large. Ivabradine does not therefore seem to have an impact, in comparison with placebo, on the quality of life of patients treated for heart failure.

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4 Questions based on Likert scales (with 5, 6 or 7 items) provide information on several different areas (functional limitations, symptom frequency, severity and change over time, efficacy, quality of life, social limitations).<sup>5</sup> Scores from 0 to 100: the higher the score, the better the patient's health.

6 OSS = mean score from the following areas: physical limitations, symptoms, quality of life and social limitations.

7 CSS = mean score from areas concerning functional limitations and symptoms.

## 3.2. Adverse effects

### 3.2.1. Data from clinical trials

In the SHIFT study, 4806/6492 patients (74%) exhibited adverse effects: 2414 (74.7%) in the PROCORALAN group versus 2392 (73.4%) in the placebo group. The most commonly reported adverse effects (> 5%) were:

- Heart failure: 701 patients (21.7%) versus 846 patients (26%);
- Atrial fibrillation: 267 (8.3%) versus 217 (6.7%);
- Uncontrolled blood pressure: 228 (7.1%) versus 198 (6.1%);
- Slowing of heart rate: 181 (5.6%) versus 45 (1.4%).

Serious adverse events were observed in 42.4% of patients in the PROCORALAN group and 45.4% in the placebo group. The most common serious adverse events were:

- Cardiac disorders (primarily heart failure, atrial fibrillation): 26.4% versus 28.8%;
- Infections (especially pneumonia): 5.5% versus 6.1%.

According to the SPC, the adverse effects most commonly observed with PROCORALAN are phosphenes and bradycardia.

### 3.1.2. Data from PSURs

Analysis from the most recent periodic safety update report (PSUR) covering the period from 25 October 2005 to 25 December 2009 estimates the exposure of patients to treatment, in the indication of stable angina, as 238,463 patients-years. In total, during this period, 647 corresponding pharmacovigilance cases were reported, of which 314 were serious. The most common adverse effects were:

- eye disorders: phosphenes (56), blurred vision (13), vision disorders (25);
- bradycardia (73), including 14 cases of excessive bradycardia;
- supraventricular tachycardia (39) including 28 cases of fibrillation and six cases of flutter.

During this period, 42 deaths were also observed.

Three revisions to the marketing authorisation were made during and following this period, involving section 4.8 (adverse effects):

- on 05/05/2009, comprising the addition of prolonged QT interval on ECG;
- on 29/11/2010, comprising the addition of rash, erythema, pruritus, hypotension, malaise and syncope (possibly related to bradycardia);
- on 26/08/2011, comprising the addition of angioedema, urticaria and asthenia possibly related to bradycardia.

This proprietary medicinal product is subject to a risk management plan, including monitoring of the following risks in particular:

- Identified risks:
  - o bradycardia;
  - o phosphenes and blurred vision;
  - o atrioventricular block;
  - o increased blood pressure in hypertensive patients;
  - o atrial fibrillation.
- Potential risks:
  - o supraventricular tachycardia;
  - o immune disorders.
- Missing information: the effect of ivabradine in children and adolescents (< 18 years), in pregnant and lactating women, in patients with severe hepatic insufficiency or severe renal impairment, and in chronic heart failure patients with intraventricular conduction defects.

Finally, two studies are currently underway as part of this risk management plan:

- study CL3-083 (SIGNIFY), the aim of which is to evaluate the efficacy of ivabradine in stable coronary artery disease patients without heart failure (expected to conclude Q4 2013);
- study CL3-067, the aim of which is to evaluate the long-term ophthalmic effects (three years) and cardiovascular efficacy of ivabradine in patients with angina (expected to conclude Q4 2015).

### 3.3. Conclusion

Ivabradine (PROCORALAN) has been evaluated in its “heart failure” extension of indication in a placebo-controlled trial (SHIFT) in 6505 patients with stable heart failure.

Ivabradine was superior to placebo in reducing the primary endpoint, a composite of cardiovascular deaths including deaths of unknown origin or the first hospitalisation for worsening heart failure: 24.5% versus 28.7% events: HR = 0.82 [0.75; 0.90],  $p < 0.0001$ .

This difference is primarily due to a reduction in first hospitalisations for worsening heart failure: 15.9% versus 20.6%, HR = 0.74 [0.66; 0.83],  $p < 0.0001$ , whereas cardiovascular mortality was not significantly reduced (13.9% versus 15%, HR = 0.91 [0.80; 1.03]).

Efficacy was also evaluated in different subgroups, including subgroups determined *a priori* by heart rate  $\geq 77$  or  $< 77$  bpm and by whether or not beta-blockers were taken.

Ivabradine was superior to placebo at reducing the primary endpoint only in patients with a heart rate  $\geq 77$  bpm (HR = 0.75 [0.67; 0.85],  $p < 0.0001$ ). In these patients, ivabradine was also superior to placebo for reducing cardiovascular mortality: HR = 0.81 [0.69; 0.96],  $p = 0.0137$ . For information purposes, in patients with a heart rate  $\geq 77$  bpm, a subgroup was defined *a posteriori* according to whether or not ivabradine was combined with a beta-blocker. A significant reduction in the primary endpoint was observed in both groups (treated or not with beta-blockers). Although a significant reduction in hospitalisations for worsening heart failure was observed in patients treated or not with beta-blockers, a significant reduction in cardiovascular mortality was only observed in the group of patients not treated with beta-blockers: HR 0.50 [0.34; 0.76].

In the subgroup of patients determined *a priori* by whether or not beta-blockers were taken, a significant reduction in the composite primary endpoint, combining cardiovascular deaths (including deaths of unknown origin) or the first hospitalisation for worsening heart failure, was observed in both predefined groups: patients treated with beta-blockers: 0.85 [0.76; 0.94], and patients not treated with beta-blockers: 0.68 [0.52; 0.88]. In these patients, although a significant reduction in first hospitalisations for worsening heart failure was observed in both groups, a significant reduction in cardiovascular mortality was only observed in the group of patients not treated with beta-blockers: HR 0.72 [0.52; 1.00].

Taking into account the small number of class IV patients included in this study (111, i.e. 1.7%), the efficacy of PROCORALAN in these patients cannot be established.

No studies have compared ivabradine with other medicines indicated in patients with heart failure in combination with standard treatments.

The adverse effects most commonly observed with ivabradine (PROCORALAN) are cardiac (atrial fibrillation, uncontrolled blood pressure, bradycardia, prolonged QT interval) and visual (phosphenes).



## 4. TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Stable heart failure is a disorder that can progress to more advanced and severe stages. Its complications can be life-threatening.

These proprietary medicinal products are intended as curative therapy.

In the SHIFT study, the efficacy of PROCORALAN was demonstrated on the composite primary endpoint combining hospitalisations for heart failure and cardiovascular deaths. Nonetheless, its efficacy on each of the components of the primary endpoint (hospitalisations for heart failure and cardiovascular deaths) was only demonstrated in a subgroup of patients defined *a priori*: heart failure patients with systolic dysfunction, sinus rhythm and a heart rate  $\geq 77$  bpm, and especially those not treated with beta-blockers (due to contraindication or intolerance). Furthermore, only 2% of patients included in this study had class IV heart failure; therefore, the efficacy of PROCORALAN in these patients cannot be ascertained.

In these patients, the efficacy/adverse effects ratio is high.

Alternative therapeutics are available.

These proprietary medicinal products are second-line drugs, in patients with heart failure who still have an elevated heart rate despite optimised treatment (including ACE inhibitors or ARBs, diuretics, aldosterone antagonists and cardiac glycosides if required) and in those for whom beta-blockers are contraindicated or poorly tolerated.

#### Public health benefit:

Chronic heart failure of NYHA classes II-IV with systolic dysfunction is a common and serious pathological condition. For this new indication, as the population likely to benefit from this treatment is undoubtedly limited, its impact on public health can be considered to be moderate.

Reducing mortality and re-hospitalisations for acute decompensation in patients with chronic heart failure, and improving their quality of life, is a public health need (GTNDO report, 2003).

Taking into account the results of the SHIFT study, an impact on morbidity in the treated population is expected. In contrast, an impact on cardiovascular mortality was only demonstrated in the subgroup of patients with a heart rate greater than 77 bpm.

Nonetheless, it is not certain whether these results are transferable to actual conditions of use, due to doubts regarding the use of beta-blockers and the doses used.

In terms of the impact on healthcare organisations, a reduction in hospitalisations for worsening heart failure is expected.

Consequently, a public health benefit is expected from the proprietary medicinal product PROCORALAN in the indication "chronic heart failure", although this benefit is slight.

The actual benefit of these proprietary medicinal products is substantial.

#### 4.2. Improvement in actual benefit (IAB)

Taking into account the results of the SHIFT study, PROCORALAN offers a minor improvement in actual benefit (IAB IV) in the therapeutic strategy and only in patients with stable class II to III heart failure with systolic dysfunction, sinus rhythm and a heart rate  $\geq 77$  bpm in whom beta-blockers are contraindicated or poorly tolerated.

In other patients, PROCORALAN does not offer any improvement in actual benefit (IAB V).

#### 4.3. Therapeutic use<sup>8</sup>

The management of patients with mild, moderate or severe heart failure, with reduced systolic ventricular function (ejection fraction  $\leq 40\%$ ), combines the prescription of a loop diuretic, an angiotensin-converting enzyme inhibitor and a cardiac glycoside in the majority of cases; the prescription of a beta-blocker (bisoprolol, carvedilol, metoprolol or nebivolol) should be considered in patients with “stable” heart failure. This enables to achieve an additional reduction in mortality.

For patients with NYHA stage III or IV heart failure, the addition of low-dose spironolactone (25 to 50 mg/day) leads to a reduction in overall mortality and cardiovascular mortality, as well as in the risk of hospitalisation for worsening heart failure; in this case, serum potassium should be  $< 5.5$  mmol/l and blood creatinine  $< 220$   $\mu$ mol/l.

Taking into account the results of the SHIFT study, PROCORALAN should be limited to patients with class II to III heart failure with systolic dysfunction, sinus rhythm, heart rate  $\geq 77$  bpm despite optimised treatment, and in whom beta-blockers are contraindicated or poorly tolerated.

#### 4.4. Target population

The target population of PROCORALAN in its extension of indication corresponds to patients with stable NYHA class II to III heart failure with systolic dysfunction, sinus rhythm and a heart rate greater than or equal to 77 bpm, in whom beta-blockers are contraindicated or poorly tolerated.

It can be estimated from the following data:

- According to ESC 2008,<sup>9</sup> the prevalence of heart failure is estimated to be between 2% and 3% of the general population. Almost half of patients with heart failure are thought to have a reduced ejection fraction, i.e. between 660,000 and 990,000 individuals in France.
- Almost a quarter of patients are thought to have associated atrial fibrillation.<sup>10</sup> It is therefore estimated that between 500,000 and 750,000 people in France have heart failure with systolic dysfunction and sinus rhythm.
- In the EURObservational Research Programme study,<sup>11</sup> out of all patients included with heart failure, 37% had a heart rate  $\geq 75$  bpm.

Therefore, the number of patients with chronic heart failure with systolic dysfunction and sinus rhythm whose heart rate is greater than or equal to 75 bpm can be estimated as between 180,000 and 280,000.

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8 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).

9 Dickstein K 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: 2388–2442.

10 de Groote P et al. Improvement in the management of chronic heart failure since the publication of the updated guidelines of the European Society of Cardiology. The Impact-Reco Programme. Eur J Heart Fail 2009; 11: 85–91.

11 Maggioni AP, EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF). Complementary analyses from ESC-HF Pilot database according to heart rate threshold in patients with chronic heart failure. With permission of the ESC EORP Executive Committee 2012.

The epidemiological data available do not allow to quantify with precision those patients with a heart rate  $\geq 77$  bpm and in whom beta-blockers are contraindicated or poorly tolerated, who correspond to the population most likely to benefit from treatment with PROCORALAN. For information purposes, on the basis of two recent French studies, between 23% and 30% of patients with chronic heart failure do not receive beta-blockers.<sup>10,12</sup>

#### **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 indication “treatment of chronic heart failure, NYHA class II to IV with systolic dysfunction, in patients in sinus rhythm and whose heart rate is  $\geq 75$  bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated”.

4.5.1. Packaging: Appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65%

4.5.3. Request for study

It is difficult to quantify the population likely to benefit most from the product, i.e. the subgroup of patients with a heart rate greater than 77 bpm, sinus rhythm, class II or III heart failure with systolic dysfunction, and a contraindication or intolerance to beta-blockers.

It is therefore essential to describe all patients treated with PROCORALAN for heart failure in actual practice, and to identify the percentage of patients meeting the criteria above and those receiving beta-blockers at an optimal dose.

The Transparency Committee therefore hopes to receive additional data on the proprietary medicinal product PROCORALAN, in the indication “chronic heart failure”, gathered under conditions of actual use, and which can describe the patients treated (age, gender, description of disease (class, ventricular function, heart rate, etc.), previous treatments (dosage adjustments, reason for discontinuation), reason for prescription of PROCORALAN, and concomitant treatments (duration, dosage, etc.)).

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12 Cohen Solal A et al. Optimization of heart failure medical treatment after hospital discharge according to left ventricular ejection fraction: the future survey. Archives of cardiovascular disease. 105, 355-365. 2012.