06 November 2014
EMA/734305/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Review under Article 20 of Regulation (EC) No 726/2004,

Invented name(s): Corlentor and Procoralan

INN: ivabradine

Procedure numbers: Corlentor EMEA/H/A20/1404/C/000598/0031
Procoralan EMEA/H/A20/1404/C/000597/0032

Note

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

On 30 April 2014, the EMA received from the MAH a communication on the preliminary results of the SIGNIFY[1] study. The SIGNIFY is a multicentre, randomised, double-blind, parallel-group, placebo-controlled, event-driven study which was designed to test the hypothesis that heart rate lowering with ivabradine reduces cardiovascular (CV) event rates in patients with stable coronary artery disease (CAD) without clinical heart failure. This study used doses of ivabradine higher than the currently recommended in the product information (starting dose in SIGNIFY: 7.5 mg twice daily [5 mg twice daily if age≥75 years], that could be increased up to 10 mg twice daily).

In the whole population (n=19102), ivabradine did not significantly affect the primary composite endpoint (PCE) or its individual components (CV death and non-fatal myocardial infarction). However, in the pre-specified subgroup of symptomatic angina patients (CCS class II or higher) (n=12049), a statistically significant increase in PCE was observed (HR=1.18; 95%CI [1.03-1.35]). Although not reaching statistical significance, similar trends were observed for the individual components of CV death and non-fatal myocardial infarction (MI). These findings appear contradictory with findings from previous ivabradine studies in patients with CAD.

Given that the subgroup of symptomatic angina patients may correspond to the population of patients for whom one of the therapeutic indications for ivabradine is currently approved, the European Commission initiated on 8 May 2014 a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the Agency to assess the above concerns and their impact on the benefit-risk balance of the centrally authorised medicinal products Procoralan and Corlentor (both containing ivabradine). The European Commission requested the Agency to give its opinion on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn.

2. Scientific discussion

Ivabradine is a heart rate lowering agent with specific effect on the sinus node with no effects on intra-atrial, atrioventricular or intraventricular conduction times, myocardial contractility or ventricular repolarisation.

Ivabradine selectively blocks the f-channel in the pacemaker cells of the sinus node by entering and binding to a site in the channel pore. By inhibiting ion flow through the f-channel, ivabradine reduces the f-current (If) thus reducing the slope of the slow diastolic depolarisation phase of the action potential in the sinus node cells, thereby increasing the time required to reach the voltage threshold for action potential initiation. This in turn slows the spontaneous firing of sino-atrial node cells and therefore the heart rate. Electrophysiological studies in sino-atrial node cells have demonstrated that, at therapeutic doses, ivabradine does not act on any other cardiac ion currents (IK, ICaL or ICaT). Ivabradine exerts a pure heart rate lowering effect without any direct effect on myocardial contractility and relaxation, cardiac output, coronary haemodynamics, blood pressure and peripheral resistance.

Since the Marketing Authorisation for both medicinal products was granted and up until 25 October 2013, the estimated exposure to ivabradine in EU countries is 1,194,720 patient-years and approximately 0.4 million patient-years outside the EU. The product is authorised as 5 mg and 7.5 mg tablets.

[1] Study assessInG the morbi-mortality beNefits of the I_f inhibitor ivabradine in patients with coronary arterY disease.

Regulatory history

Ivabradine was granted a marketing authorisation in October 2005 for the indication "symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who have a contraindication or intolerance for beta-blockers".

On the basis of efficacy and safety data from studies that became available after the initial marketing authorisation including the BEAUTIFUL[2] study, the indication was extended in October 2009 to include combination with beta-blockers in patients whose angina is inadequately controlled with an optimal beta-blocker dose and whose heart rate is >60 bpm. In angina, the usual recommended starting dose of ivabradine is 5 mg twice daily (b.i.d) and 2.5 mg b.i.d. for patients over 75 years of age. After three to four weeks of treatment, the dose may be increased to 7.5 mg twice daily depending on the therapeutic response.

In February 2012, ivabradine was approved for the treatment of heart failure in the European Union based on the results of the SHIFT[3] study. This indication concerns use in chronic heart failure New York Heart Association (NYHA) class II to IV with systolic dysfunction, in patients in sinus rhythm with heart rate ≥75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

Ivabradine is approved for use in 102 countries worldwide for the treatment of chronic stable angina and 88 countries for the treatment of chronic heart failure.

2.1. Clinical aspects

This review was triggered on the basis of the preliminary results of the SIGNIFY study. The full clinical study report was provided during the current review and the study results were published[4] while the review was ongoing.

2.1.1. The SIGNIFY study

Objectives

The primary objective was to demonstrate the superiority of ivabradine compared to placebo in the reduction of CV mortality or non-fatal MI (composite endpoint).

The secondary objectives were to assess the effect of ivabradine compared to placebo in the reduction of the non-composite endpoints, including all-cause mortality, CV mortality, coronary death, non-fatal MI, coronary revascularisation (elective or not), elective coronary revascularisation, new onset or worsening heart failure; as well as on other composite endpoints.

Other objectives included the change in angina symptoms using the classification of the Canadian Cardiovascular Society (CCS) in patients with angina symptoms at baseline; change in heart rate; and the assessment of safety.

Methodology

The target population was adult patients with stable CAD without clinical heart failure, receiving all treatments appropriate to their CV condition.

[2] MorBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction.
[3] Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial.
[4] Fox K, et al. Ivabradine in stable coronary artery disease without clinical failure. N Engl J Med 2014;371:1091-9.

This was a randomised, double-blind, placebo-controlled, multicentre, international, event-driven, morbidity-mortality study, with two parallel and balanced treatment arms conducted at 1139 centres in 51 countries. The randomisation was stratified by centre and on whether or not the patients were in CCS class II or higher at selection and inclusion visits. The study has been designed to continue until at least 1070 primary events had occurred and the last patients included had been followed-up for 18 months.

Diagnosis and main criteria for inclusion

The main selection and inclusion criteria were: male or female aged ≥ 55 years, evidence of CAD, sinus rhythm and resting heart rate ≥ 70 bpm on 2 consecutive resting 12-lead ECGs performed at least 5 minutes apart, preserved left ventricular systolic function, ambulatory and in stable condition with respect to angina and on appropriate and stable doses of conventional CV medications, presence of at least one major CV risk factor or at least two minor CV risk factors and written informed consent obtained.

The main exclusion criteria were: unstable CV condition and clinical signs and/or symptoms of heart failure in NYHA class II or higher, or hospitalisation for heart failure as a primary diagnosis within the last 12 months.

Study drug

At inclusion, patients received ivabradine 7.5 mg b.i.d. or placebo, except for patients aged ≥ 75 years at selection (who were initiated at 5 mg b.i.d.). Follow-up visits occurred at 1, 2, 3 and 6 months and every 6 months thereafter. This study drug could be adjusted to 5, 7.5 or 10 mg b.i.d. according to the heart rate as measured by electrocardiography at every visit (target heart rate 55 to 60 beats per minute) and symptoms of bradycardia. If a patient was already on 5 mg b.i.d., study treatment was stopped if the heart rate was less than 45 bpm or if there were symptoms of bradycardia, or if they had a heart rate of less than 50 bpm that persisted at a newly scheduled control visit 1 week later.

Following a run-in period of 14 to 30 days during which placebo was dispensed to patients in a single-blind way, the active double-blind treatment period lasted from 18 months to 48 months.

Disposition of patients

The disposition of patients is shown in table 1.

Table 1 - Disposition of patients in the SIGNIFY study

Status	Ivabradine		Placebo		All	
	n	%	n	%	n	%
Included and randomised	**9550**	**100**	**9552**	**100**	**19102**	**100**
Study completed	8830	92.5	8894	93.1	17724	92.8
Adverse event leading to death	485	5.1	458	4.8	943	4.9
Consent withdrawal	231	2.4	199	2.1	430	2.3
Withdrawn by sponsor's decision*	1	< 0.1	-	-	1	< 0.1
Lost to follow-up	3	< 0.1	1	< 0.1	4	< 0.1
Randomised Set (RS)	**9550**	**100**	**9552**	**100**	**19102**	**100**
Safety Set (SS)	9539	99.9	9544	99.9	19083	99.9
RS_{ANG}	6037	63.2	6012	62.9	12049	63.1
SS_{ANG}	6030	63.1	6009	62.9	12039	63.0

n: Total number of patients in the considered treatment group; % = % of total number of patients treatment group
** Upon request from a local ethics committee further to recent diagnosis of Alzheimers disease in this patient, during the study*

The two groups were well balanced with respect to baseline characteristics.

Summary of efficacy results

There was no significant difference in the incidence of the primary endpoint between the ivabradine group and the placebo group (6.8% and 6.4%, respectively; HR=1.08, 95% CI [0.96 -1.20]; p=0.2). There were also no significant differences between the two groups in the incidences of the components of the primary composite endpoint (death from CV causes and nonfatal MI). No significant differences were also observed in any of the secondary endpoints.

Several pre-specified subgroup analyses were performed and the only significant interaction identified was in the incidence of the primary composite endpoint in the angina CCS class ≥ II patients (RS_{ANG}) (table 2).

Table 2 - Incidence of the primary composite endpoint and its components in RS_{ANG}

	Ivabradine (N = 6037)				Placebo (N = 6012)				Hazard ratio			
	NPY	n	%	%PY	NPY	n	%	%PY	E	SE	95% CI	p-value
Primary composite endpoint	13625	459	7.60	3.37	13633	390	6.49	2.86	1.18	0.08	[1.03-1.35]	0.0176
Secondary endpoints												
Cardiovascular death	13921	245	4.06	1.76	13898	210	3.49	1.51	1.16	0.11	[0.97-1.40]	0.1053
Non-fatal MI	13625	235	3.89	1.72	13633	200	3.33	1.47	1.18	0.11	[0.97-1.42]	0.0918

N: number of patients at risk; NPY: number of patient-years; n: number of patients having experienced the endpoint
%: global incidence rate; %PY: (n/NPY) x100; E: estimate of the hazard ratio between treatment groups (Ivabradine/Placebo) on unadjusted Cox proportional hazards model;; SE: standard error of the hazard ratio; 95% CI: 95% Confidence Interval of the estimate (two-sided); p-value: Wald test

Summary of safety results

The summary of incidence of emergent adverse events (EAEs) by category and seriousness is presented in table 3.

Table 3 - Overall summary of safety results in the safety set of SIGNIFY

On-treatment events (unless stated)	Ivabradine (N = 9539)			Placebo (N = 9544)		
	n	%	%PY	n	%	%PY
Patients having reported at least one:						
Emergent adverse event	6920	72.5	35.3	6321	66.2	30.6
Severe emergent adverse event	1309	13.7	6.7	1300	13.6	6.3
Treatment-related emergent adverse event	2437	25.5	12.4	557	5.8	2.7
EAE of bradycardia (all forms)	1703	17.9	8.7	202	2.1	1.0
EAE of phosphenes	509	5.3	2.6	51	0.5	0.2
Patients having experienced at least one:						
Serious emergent adverse event (including death)	3379	35.4	17.3	3263	34.2	15.8
Serious treatment-related emergent adverse event	269	2.8	1.4	60	0.6	0.3
Patients with treatment withdrawal due to:						
Emergent adverse event	1247	13.1	6.4	699	7.3	3.4
EAE of bradycardia (all forms)	381	4.0	1.9	45	0.5	0.2
EAE of phosphenes	61	0.6	0.3	11	0.1	0.1
Serious emergent adverse event	629	6.6	3.2	475	5.0	2.3
Fatalities						
EAE with fatal outcome	363	3.8	1.9	356	3.7	1.7
All-cause mortality (during the study)	498	5.2	2.3	466	4.9	2.1

N: total number of patients in considered treatment group; NPY: 19582.7 in the ivabradine group; 20685.6 in the placebo group
n: number of affected patients; % = (n/N) x 100; %PY = (n/NPY) x 100

The safety profile was dominated by adverse reactions already described for the product, notably all forms of bradycardia (17.9% ivabradine vs 2.1% placebo) and phosphenes (5.3% ivabradine vs 0.5% placebo). Atrial fibrillation (AF) occurred in 5.3% of patients on ivabradine vs. 3.8% of patients on placebo during the study.

2.1.2. Discussion of the SIGNIFY study results

Efficacy of treatment with ivabradine has previously been shown in terms of symptomatic improvement in CAD patients with angina.

An overall beneficial effect on CV outcomes could not however be demonstrated. In patients with CAD without clinical heart failure and baseline HR ≥70 bpm (SIGNIFY study (n=19102)), using higher doses than currently approved, the primary composite of CV death and non-fatal MI showed no significant difference between-groups.

In the pre-specified subgroup of angina patients in SIGNIFY (defined as patients with CCS class II or higher), ivabradine increased the incidence of the primary composite of CV death or non-fatal MI (7.6% versus 6.5% with placebo, HR=1.18, 95% CI: 1.03-1.35, p=0.018) (table 2), a small absolute difference of 69 events was observed, mainly MI. Due to this small absolute risk, subgroup analyses are complicated. Nevertheless, several analyses were performed in an attempt to explore and explain the results observed.

In SIGNIFY, the rate of CCS class improvement in patients with angina symptoms at baseline was significantly higher in the ivabradine group with 1589/6900 improved patients (23.0%) versus 1256/6909 (18.2%) for placebo at the 3rd visit and was maintained at the last visit (36.8% in the ivabradine group versus 34.1% in the placebo group).

Dose profile, influence on heart rate and PCE risk

The randomised angina set (n=12049) consisted of 90% younger patients (<75 years) and 10% older patients (≥75 years) (figure 1).

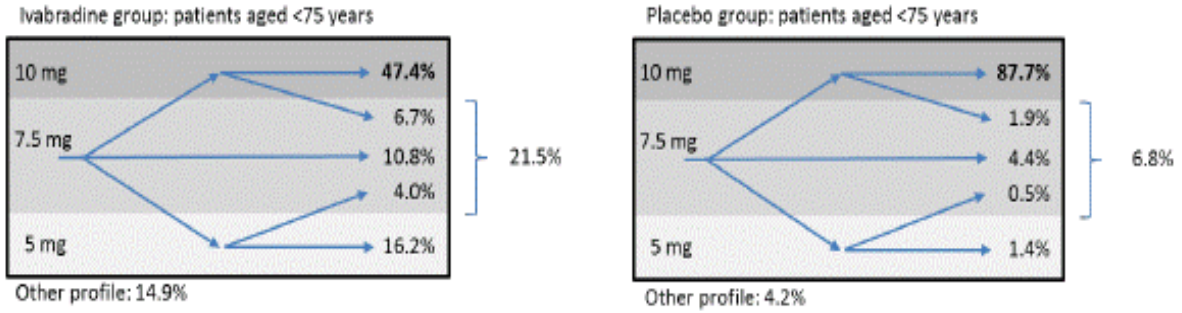

Figure 1 - Main dose profiles in patients aged < 75 years - randomised set angina patients

The mean dose administered to patients aged <75 years in the ivabradine group was 8.3 ± 1.7 mg (median: 8.9). In the placebo group, the mean "dose" was 9.6 ± 0.8 mg (median: 9.9).

In patients aged ≥75 years in the ivabradine group, the mean dose was 7.3 ± 1.9 mg (median: 7.3). In the placebo group, the mean "dose" was 8.9 ± 1.5 mg (median: 9.6).

The highest reduction of heart rate was shown with the lowest dose of ivabradine and the lowest reduction with the highest dose (table 4).

Table 4 - 12 lead ECG heart rate achieved and heart rate change during the study according to the dose prescribed for the longest period

Dose prescribed	N	Baseline HR, bpm	M3 HR, bpm	HR change, M3-baseline, bpm
Placebo group	9552	77.2 (7.1)	70.7 (10.1)	-6.6 (9.8)
5 mg group	2100	75.0 (5.0)	55.5 (7.6)	-19.5 (8.4)
7.5 mg group	2584	75.9 (5.8)	58.1 (7.6)	-17.6 (8.6)
10 mg group	4854	78.7 (7.7)	64.6 (8.9)	-14.2 (10.2)

Numbers are mean (SD)

From 40 bpm onwards, the lowest risk of PCE was observed with the lowest heart rate achieved (40-50 bpm) and PCE risk increased with higher heart rate. Similarly, the greater the reduction in heart rate, the lower was the PCE risk.

Table 5 - Primary endpoint in the ivabradine group according to the lowest heart rate achieved on treatment

	SS - Ivabradine group (N=9539)			SS Angina subgroup - Ivabradine group (N=6030)		
	N	Event rate, n(%)	Hazard ratio (95% CI)	N	Event rate, n(%)	Hazard ratio (95% CI)
Primary composite endpoint						
< 40 bpm	111	6 (4.4%)	1.86 (0.82-4.24)	82	5 (6.1%)	2.09 (0.84-5.17)
[40 ; 50[bpm	3420	119 (3.5%)	1.00	2128	76 (3.6%)	1.00
[50 ; 60 [bpm	4530	273 (6.0%)	1.58 (1.27-1.97)	2862	194 (6.8%)	1.73 (1.32-2.26)
[60 ; 70[bpm	1083	78 (7.2%)	2.10 (1.56-2.82)	694	61 (8.8%)	2.45 (1.73-3.47)
≥ 70 bpm	216	19 (8.8%)	3.40 (2.05-5.66)	147	13 (8.8%)	3.09 (1.67-5.71)

The absolute risk between ivabradine and placebo on the primary endpoint was 1% (7.6% in ivabradine versus 6.5% in placebo) in the angina subset (see table 2). Furthermore, in a dosage at time of event evaluation, most primary endpoints occurred at the highest dose (57.7%) compared to the 7.5 mg (26.4%) and 5 mg (15.9%), with similar results for the individual endpoints. In addition, the use of a nested structural accelerated failure time model seems to show an increased risk for "exposed to 10 mg" versus "not exposed to 10 mg" on CV endpoints (1.24 [0.88-2.10]), driven by the results in patients <75 years starting with the 7.5 mg dose (1.50 [0.93-2.40]), although results were not significant.

Baseline heart rate

Data from SIGNIFY seems to indicate that if patients were divided in tertiles of baseline HR, ivabradine is less beneficial in the patients with <75 bpm compared to patients with a higher baseline heart rate (i.e. >80 bpm) for the PCE. However, this analysis should be interpreted with caution as the p for trend is not significant and the same trend is not observed for the individual components of the PCE. When patients were divided in five groups according to baseline HR, such a trend could not be observed, however this analysis is hampered by the limited number per group.

In the BEAUTIFUL study, in a pre-specified subgroup of patients with heart rate ≥70 bpm (N=5392) (interaction statistically significant p=0.030), it was demonstrated that the increase of baseline heart rate from 60 bpm to 70 bpm provides additional safety in terms of CV outcomes and particularly for PCE and MI (fatal or not) when comparing patients with baseline heart rate <70 bpm versus baseline heart rate >70 bpm: PCE: HR 1.13, 95% CI: 0.98-1.31 versus 0.91 [0.81-1.04], respectively, and for MI (fatal or not): 1.19 [0.91-1.56] versus 0.64 [0.49-0.84], respectively. Similar results were observed in the subgroup of patients with limiting angina symptoms at baseline (N=1507); PCE: 0.85

[0.57-1.26] versus 0.69 [0.47-1.01], respectively, and MI (fatal or not): 0.86 [0.49-1.50] versus 0.27 [0.11-0.66], respectively.

Heart rate achieved on treatment

In SIGNIFY, patients who achieved a heart rate <50 bpm during treatment with ivabradine had a non-significant increased risk of CV outcomes when compared to placebo, although this finding was based on a limited number of patients. The majority of the patients with a primary composite endpoint had their lowest heart rate (<50) more than 6 months before the occurrence of the event. No difference in the reduction in mean heart rate was observed when matching patients treated with ivabradine with MI compared to patients treated with ivabradine without MI. In addition, no clear trend is observed for this mean heart rate in relation to the treatment effect for the primary composite endpoint, with inconsistent results for the individual components of the primary composite endpoint. In a time-varying Cox model, a trend for a higher risk for patients achieving a low heart rate could not be observed.

Interaction with CYP 3A4 inhibitors with heart rate reducing properties

The metabolism of ivabradine occurs via CYP 3A4 only. Ivabradine is a competitive but very weak inhibitor of CYP 3A4 and as such it does not influence the pharmacokinetics of other substrates of CYP 3A4 (mild, moderate or strong inhibitors). However, the pharmacokinetics of ivabradine is modified by strong and moderate CYP 3A4 inhibitors. Strong inhibitors like ketoconazole or macrolide antibiotics may increase the exposure of ivabradine by 7- to 8-fold for the AUC and by 3- to 4-fold for the C_{max} and are contra-indicated with ivabradine. Moderate CYP 3A4 inhibitors with heart rate lowering properties (diltiazem and verapamil) may increase ivabradine exposure by a factor of 3.

The concomitant administration of moderate CYP 3A4 inhibitors with heart rate lowering properties (diltiazem and verapamil) was allowed in SIGNIFY and there were no specific instructions regarding ivabradine dose regimen in the concerned patients. A substantial number of patients (7.3% in ivabradine group and 6.9% in the placebo group) were receiving diltiazem or verapamil or strong CYP 3A4 inhibitors at inclusion, or during the study.

In patients having taken at least diltiazem, verapamil or other CYP 3A4 inhibitors during the study, ivabradine was associated with a significantly worse outcome for the primary endpoint (risk increased by 43%, interaction p-value=0.062) and non-fatal MI (risk increased by 64%, interaction p-value=0.006). In the angina subset, the outcome was significantly worse for the primary endpoint (risk increased by 62%, interaction p-value=0.088) and non-fatal MI (risk increased by 88%, interaction p-value=0.026).

Despite starting with a higher heart rate, the incidence of bradycardia in the group of patients taking diltiazem, verapamil or strong CYP 3A4 inhibitors was higher than in the overall population: 20.4% vs. 17.9%, respectively.

Other potential statistical interactions

In the SIGNIFY study, the effect of ivabradine on the PCE and its components for different angina classes remains uncertain. For the composite of fatal or non-fatal MI, there was a significant interaction between the effect of ivabradine and the angina symptoms at baseline for subgroups CCS class ≥ II versus CCS class < II. However, this was no longer significant for angina symptoms at baseline (i.e. in CCS class ≥ I) vs no angina symptoms at baseline (p-value for interaction p=0.78) and no trend was observed across the individual angina classes.

A low diastolic blood pressure (DBP) <60 mm Hg, reported at any time during the study showed a significant increased risk for MI (and also the primary endpoint) compared to the 70-80 mmHg category (2.09 [1.30-3.37]). However, from another analysis it seems unlikely that the PCE result could have been caused by a DBP <60 mm Hg as the majority of the patients with a PCE had their lowest DBP more than 6 months before the occurrence of the event.

A low systolic blood pressure did not increase the CV risk. Also no relation between pulse pressure and outcome could be observed.

In general, evaluation of several baseline characteristics for the secondary endpoints did not reveal any interaction which would identify patients at higher risk for treatment of ivabradine, except for an interaction of age on MI. Patients <65 years showed a higher risk for MI than patients ≥65 years with a significant p-value for interaction (p=0.035).

No interaction for CV endpoints was observed for baseline use of amiodarone, dihydropyridine CCBs, and beta-blocker. Beta-blocker use during treatment also showed no interaction.

Bradycardia

Bradycardia and visual symptoms are the main adverse effects related to the mechanism of action.

For the SIGNIFY study, bradycardia occurred in 17.9% (n=1703) vs 2.1% (n=202) patients, which was higher than in patients with HR ≥70 in the BEAUTIFUL trial (4.0% (n=109) vs 1.2% (n=31)) and in heart failure patients in the SHIFT study (10% (n=322) vs 2.2% (n=72)).

For angina patients in the SIGNIFY study, bradycardia occurred in 17.9% on ivabradine and 2.5% on placebo, while in the subgroup of patients with angina and heart rate ≥70 in the BEAUTIFUL study this was 4.6% (n=16) and 1.7% (n=6), respectively.

The use of a nested structural accelerated failure time model displayed a higher risk for bradycardia for patients exposed to 10 mg dose versus not exposed to 10 mg (E=2.54; 95% CI: 1.54-4.82), mainly driven by patients with starting dose of 7.5 mg as for patients ≥75 years of age, all starting on 5 mg, had a E of 0.57 [0.06-1.57] suggesting a more limited risk of emergent bradycardia on 10 mg dose when ivabradine is started at 5 mg dose.

More bradycardia events on the 10 mg dose were demonstrated in 2 small parallel studies. One study with forced titration from 5 to 7.5 mg or 5 to 10 mg, showed respectively 2.2% vs 5.4% events of bradycardia. The other study comparing 7.5 vs 10 mg showed 6.5% vs 10.5%. This latter study also displayed a higher bradycardia incidence probably due to the higher number of patients on the 7.5 mg starting dose.

Atrial fibrillation

In SIGNIFY, AF occurred in 5.3% of patients on ivabradine vs. 3.8% of patients on placebo, during the study. In a pooled analysis of controlled double blind studies a significant increased risk for AF 1.26 (1.15-1.39), with a higher frequency (4.86% vs 4.08%) was found. In the SIGNIFY study, for patients with atrial fibrillation on treatment, the proportion of patients with a subsequent primary endpoint was similar in the ivabradine group (11.5% per year) and in the placebo group (10.8% per year). These observations do not seem to provide a clear explanation for the observed increased CV risk in SIGNIFY.

2.2. Risk minimisation activities

The PRAC requested the submission of an updated Risk Management Plan including a risk minimisation plan.

A Direct healthcare professional communication (DHPC) warning prescribers of the preliminary results of SIGNIFY was sent out shortly after the review was initiated. The PRAC considered that another DHPC is required to inform prescribers of the outcome of the review and of the new recommendations (see section 5. Action Plan).

2.3. Product Information

The Product Information for Corlentor and Procoralan was revised to include the following:

- In symptomatic treatment of chronic stable angina pectoris, treatment should only be initiated in patients with HR ≥ 70 bpm. Treatment should be discontinued if the symptoms of angina do not improve within 3 months.
- Reinforcement of the recommendation not to exceed the authorised posology.
- Concomitant treatment with moderate CYP3A4 inhibitors with heart rate reducing properties such as diltiazem or verapamil is now contraindicated.
- Warnings added on measurement of heart rate, lack of benefit on clinical outcomes, and atrial fibrillation.
- Concomitant use of grapefruit juice (previously to be used with precaution) is now not recommended due to the potential for a pharmacokinetic interaction resulting in increased exposure to ivabradine.
- Update to the frequency of atrial fibrillation.
- A summary of the results of the SIGNIFY study has been added.

Amendments have been introduced to sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, and 5.1 of the Summary of Product Characteristics (SmPC). The Package Leaflet has been updated accordingly.

3. Consultation with the Scientific Advisory Group

The PRAC consulted the cardiovascular scientific advisory group (SAG) which provided advice on a number of issues.

The SAG agreed with the Rapporteurs' conclusion that there were no favourable effects observed with ivabradine on clinical outcomes and prognosis in patients with stable CAD without clinical heart failure in the SIGNIFY study. However the SAG pointed out that this is also true for other medicinal products for symptomatic treatment of CAD recommended by the European Cardiology Society (ECS) guidelines[5].

The Group noted the significant increase in the primary outcome in the pre-specified subgroup of patients in the SIGNIFY study (with angina pectoris CCS II or higher) using a dosage regimen that is not recommended in the current SmPC of ivabradine. While possible mechanisms to explain this observation such as low heart rate and low diastolic pressure have been discussed in detail, the SAG noted that this negative effect could be due to chance, given the overall neutral result of the study, the difficulty in proposing a clear pathophysiological mechanism, inconclusive results in subgroup analyses (age, angina grade, etc.) and the fact that this effect was not observed in previous studies with

[5] 2013 ESC guidelines on the management of stable coronary artery disease; European Heart Journal 2013 34, 2949-3003

ivabradine (no excess MIs in the SHIFT study). The low event rate was also considered to make it difficult to draw conclusions regarding mechanisms.

Experts agreed that the results in this subgroup raise safety concerns and supported the recommendations regarding modifications to the SmPC (dosing, HR cut-off for starting treatment, addition of the contraindication for use in patients on diltiazem and verapamil). They also agreed that the highest dosage regimen in the SIGNIFY study (max 10 mg b.i.d.) could be partly responsible for the negative results and therefore should not be recommended and that the 50 bmp cut-off for diminishing the dose/stopping the treatment should be maintained, following the explanation that a proposed cut-off of 60 bmp could possibly lead to exclusion of "responders" that particularly benefited from this therapy.

The SAG expressed concern about the considerable increase in AF rate in the SIGNIFY study. This observation is in line with former studies (in the pooled analysis of all controlled double blind studies with ivabradine a significant increase in risk of AF was found: OR 1.26 [1.15 – 1.39]). Albeit at a low absolute risk level for the observation period (4.6% vs 3.2%), it is likely that the true incidence of AF was higher - had it been thoroughly looked for by extended Holter monitoring -, which poses a major concern. The increased rate of fatal strokes in the pre-specified angina subgroup in the SIGNIFY study (26 vs 13 cases or 0.43 vs 0.22 % in the ivabradine vs placebo group) was discussed in this context. It was felt that though no proof for a causal relationship is apparent, AF might have contributed to the excess in strokes. However it is appreciated that the higher incidence of emergent AF on ivabradine vs placebo (4.6% vs 3.2%) did not translate into a higher incidence of CV events in this subgroup within the observation period of the study.

Therefore, the Group recommended to modify the SmPC by including the information that doctors should specifically look for signs and symptoms of AF and if such are found, this should be investigated further.

Given the results of the previous trials with ivabradine, the neutral results in the whole population studied in SIGNIFY, and finally the concerning findings in the subgroup of patients with angina CCS class II or higher, the Group agreed that there is a place for the treatment of symptoms with ivabradine in patients with stable angina pectoris (also with preserved left ventricular function). The SAG considered that the SmPC amendments proposed should help to diminish the risks observed in the SIGNIFY study.

It was also highlighted that patients should be informed about the benefits and risks associated with ivabradine therapy. Significant effects on symptomatic improvement (CCS class improvement at 3 months was significantly higher on ivabradine [23%] as compared to placebo [18.2%]) should be weighed against an increased CV death and MI rate (which was significant in the predefined subgroup) and against the increased rate of serious AF (3.5%, [1.7%PY] versus 2.4%, [1.1%PY]). The SAG extensively discussed the balance between symptomatic benefits and potential risks. While some members emphasised that in the main trial neither CV death nor MI rate was significantly higher in the ivabradine group, others felt that the safety signal from the angina ≥ 2 subgroup poses a major burden for this therapy. The risk of AF was, however, unequivocally seen as a concern. The Group supported the view of patients' representative that the symptomatic treatment should not be prioritised at the expense of life expectancy. Hence the recommended measures to diminish the risks observed in the SIGNIFY study.

Finally, the SAG agreed that the population studied in the SHIFT study was very different from the population studied in the SIGNIFY study (very high vs low risk for CV events; left ventricular ejection fraction (LVEF) ≤35% vs LVEF >40%; patients with NYHA class II/III vs NYHA class 0/I). The benefits

of heart rate reduction in patients with heart failure such as improved force frequency relationship, positive remodelling and others further distinguish the indication heart failure from the indication angina pectoris. Also, the dose regimen used in both studies was different. In addition, there was no signal of increased risk of MI in the SHIFT study. Therefore, the Group was of the opinion that the results of the SIGNIFY trial do not impact on ivabradine in the treatment of chronic heart failure.

4. Overall discussion and benefit/risk assessment

Ivabradine, a specific heart rate lowering agent, has demonstrated symptomatic improvement of angina symptoms in patients with stable CAD. A large study in patients with CAD and left ventricular dysfunction (BEAUTIFUL study) could not demonstrate a benefit in terms of CV outcome. The SIGNIFY study in patients with CAD without clinical heart failure using doses higher than currently approved also showed no benefit in terms of CV outcome, but demonstrated a small significant increased risk on CV outcome for patients with symptomatic angina (CCS class II or higher) in a pre-specified analysis. As the absolute risk is based on 69 events, the possibilities for further analysis to identify the contributing risk factors are limited.

Although it does not fully explain the findings, a contributor to the increased risk of CV events appears to be the high starting dose and maximum dose used in the SIGNIFY study, exceeding the currently approved maximum dose. In patients titrated to the maximum 10 mg b.i.d. dose in the SIGNIFY study (higher than the current approved 7.5 mg b.i.d.), most endpoints occurred while on the highest dose. Patients exposed to the 10 mg dose seemed to be at increased risk of a CV endpoint in comparison to patients not exposed to the 10 mg dose based on a time model evaluation. In addition, the higher dose of 10 mg could clarify the higher incidence of bradycardia during the SIGNIFY study in comparison to other large studies with ivabradine, BEAUTIFUL and SHIFT. Patients exposed to 10 mg dose versus not exposed to 10 mg showed a higher risk for bradycardia (E=2.54 [1.54-4.82]), observation supported by data from two small parallel studies also using the 10 mg dose. This highlights the need to comply with the currently authorized posology.

Although baseline heart rate ≥ 70 bpm was an inclusion criteria in the SIGNIFY study, data from the BEAUTIFUL study indicate a significant p-value for interaction for the primary composite endpoint when patient are divided around the 70 bpm cut-off level, although a significant beneficial effect was only observed for the MI endpoint in the heart rate ≥ 70 subgroup. Applying such a cut-off based on data from the BEAUTIFUL study is a reasonable measure to exclude patients who are likely to be at higher risk.

Concomitant use of diltiazem/verapamil (which also have an additional heart rate lowering effect) and strong CYP3A4 inhibitors have also shown to increase the incidence of bradycardia events and the risk of MI. Concomitant treatment with verapamil and diltiazem is currently not recommended but this should be strengthened to a contraindication to minimize the risk of clinically relevant interactions.

The increased incidence of bradycardia in relation to the increased observed CV risk upon treatment with the larger initial dose and maximum dose (as in the SIGNIFY study), or concomitant diltiazem/verapamil or strong CYP3A4 inhibitors indicate that the heart rate should not be extensively reduced. This is further supported by some of the data indicating that a heart rate <50 bpm is associated with a trend toward a higher CV risk. Therefore it is justified that ivabradine is discontinued or down titrated if the heart rate falls under 50 bpm. As a precaution, up-titration should only occur if the initial dose is well tolerated and the resting heart rate remains above 60 bpm.

Other factors could not be directly related to a higher CV risk.

The frequency of atrial fibrillation (AF) was more than currently described in the product information. However, AF was not related to the higher outcome risk as patients with AF in relation to the proportion of patients with a subsequent endpoint was similar for ivabradine as for the placebo patients. Nevertheless information monitoring of patients for AF needs to be reinforced.

In a previously evaluated clinical study on the impact of grapefruit juice on ivabradine pharmacokinetics, an intake of 600 ml given as 200 ml three times a day for 3 days a moderate interaction level was observed with a 2.3-fold increase in ivabradine exposure. Given the importance of ensuring that patients are not exposed to higher than recommended dose of ivabradine, the currently existing warning on concomitant intake of grapefruit juice should be strengthened to avoid a potential pharmacokinetic interaction.

The beneficial effect of symptomatic improvement of angina is considered of clinical relevance. However the results of SIGNIFY highlight the need to make it explicit in the product information that ivabradine use in CAD patients has no benefits on CV outcomes and it will only have an effect on symptoms of angina pectoris.

In addition to CAD, ivabradine is currently also indicated for treatment of chronic heart failure on the basis of results from the previous SHIFT study. The potential impact of the SIGNIFY results in the heart failure indication was considered, but the two populations are substantially different in terms of underlying cardiac function and presence or absence of clinical heart failure. Also a lower dose and different titration method was used in the SHIFT study when compared to the SIGNIFY study. No risk factors identified in the SIGNIFY study had an impact on the beneficial effect of ivabradine observed in the SHIFT study. Therefore it is considered that overall, the results of the SIGNIFY study do not impact on the heart failure indication.

The MAH will conduct a drug utilisation study to describe the characteristics of users of ivabradine, as well as describing the patterns of use of ivabradine and adherence to the risk minimisation measures. This will be a multinational retrospective cohort study that will collect data from medical record abstraction (chart review) for patients with chronic stable angina pectoris initiating treatment with ivabradine in routine clinical practice in selected European countries. The MAH is requested to submit within the agreed timelines, the final study protocol of the drug utilisation study. Due to the fact that the higher than approved dose used in the SIGNIFY study did not fully explain the findings of the study, it was considered key to benefit-risk balance to assess the effectiveness of the new risk minimisation measures and therefore this drug utilisation study is imposed as a condition to the marketing authorisation.

5. Action Plan

As part of this procedure, the MAH and the PRAC agreed the wording of a ‘Direct Healthcare Professional Communication’ designed to inform prescribers of the amendments to the product information of Corlentor and Procoralan, to be distributed as per the agreed communication plan.

6. Conclusion and grounds for the recommendation

Whereas

- The PRAC considered Procoralan and Corlentor (ivabradine) in the procedure under Article 20 of Regulation (EC) No 726/2004, initiated by the European Commission.

- The PRAC reviewed all data presented by the MAH on the safety and efficacy of ivabradine, including the results of the SIGNIFY study, as well as the views expressed by the cardiovascular scientific advisory group.
- The PRAC noted that the data from the SIGNIFY study showed that ivabradine does not have a beneficial effect on cardiovascular outcomes in coronary artery disease patients without clinical heart failure, and therefore its use is only beneficial for symptomatic treatment.
- The PRAC also noted a small but significant increase of the combined risk of cardiovascular death and non-fatal myocardial infarction in a subgroup of symptomatic angina patients in the SIGNIFY study. The individual components of the endpoint were not significantly increased. Ivabradine was also associated with a significantly higher risk of bradycardia. The PRAC is of the opinion that the higher than approved dose used in the SIGNIFY study does not fully explain these findings.
- The PRAC considered that the increased risks observed can be minimised by reinforcing the recommendation not to exceed the authorised posology, excluding patients with a resting heart rate < 70 bpm who are likely to be at greater risk, recommending discontinuation of treatment in the absence of improvement in angina symptoms within 3 months and contraindicating concomitant use of verapamil and diltiazem.
- The PRAC further considered data on the incidence of atrial fibrillation, which is higher than previously recognised, and concluded that ivabradine treated patients should be monitored for the occurrence of atrial fibrillation to minimise the risk of atrial fibrillation. If atrial fibrillation develops during treatment, the benefits and risks of continued treatment with ivabradine should be carefully reconsidered.
- The PRAC concluded that there are clinically relevant benefits to the symptomatic treatment of angina pectoris with ivabradine.

The PRAC is therefore of the opinion that the benefit-risk balance of ivabradine remains favourable taking into account the product information amendments and subject to the risk minimisation measures and additional pharmacovigilance activities agreed.

The PRAC has therefore recommended the variation to the terms of the marketing authorisation for Corlentor and Procoralan.