Annex IV

Scientific conclusions

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1 - PRAC recommendation

Background information

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.

Procoralan and Corlentor (both containing ivabradine) were 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[1] 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.). 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[2] 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.

On 30 April 2014, the EMA received from the MAH a communication on the preliminary results of the SIGNIFY[3] study. The SIGNIFY is a multicenter, randomized, 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). 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 (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-

[1] MorBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction.

[2] Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial.

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

risk balance of the centrally authorised medicinal products Procoralan and Corlentor. 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.

Scientific discussion

The results of the SIGNIFY study were published[4] while this review was ongoing and are discussed below.

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 Canadian Cardiovascular Society (CCS) class ≥ II patients.

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.

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 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 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.

[4] Fox K, et al, Ivabradine in stable coronary artery disease without clinical failure. N Engl J Med 2014;371:1091-9.

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 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 while on treatment with the higher initial dose and maximum dose (as in the SIGNIFY study), or concomitant diltiazem/verapamil or strong CYP3A4 inhibitors, indicates 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 atrium fibrillation (AF) was higher 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 another clinical study evaluating 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 patient 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. None of the 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.

Risk minimisation measures

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 is now not recommended due to the potential for a pharmacokinetic interaction resulting in increased exposure to ivabradine.

An additional risk minimisation activity was required by the PRAC. The MAH shall distribute a Direct Healthcare Professional Communication (DHPC) to inform prescribers of the amendments to the product information.

Furthermore a drug utilisation study shall be performed to describe the characteristics of users of ivabradine, patterns of use and assess adherence to the risk minimisation measures.

Overall conclusion

Based on the totality of the data assessed during the procedure and on the advice from the Scientific Advisory Group, the PRAC concluded that the benefit-risk balance of Procoralan/Corlentor remains favourable taking into account the product information amendments and subject to the risk minimisation measures and additional pharmacovigilance activity agreed.

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 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.

2 – Detailed explanation of the scientific differences from PRAC recommendation

Having reviewed the PRAC recommendation, the CHMP agreed with the overall scientific conclusions and grounds for recommendation.

The CHMP considered it necessary to introduce a statement in section 4.8 of the Summary of Product Characteristics reflecting the incidence of atrial fibrillation in the SIGNIFY study. Additional clarifications were also introduced in the DHPC.

CHMP opinion

The CHMP, having considered the PRAC recommendation, agrees with the overall scientific conclusions by the PRAC and is of the opinion that the marketing authorisations for Corlentor and Procoralan should be varied.