INITIATION OF THE PROCEDURE LAID DOWN IN ARTICLE 20 OF REGULATION (EC) No 726/2004

E-mail: Referral.Notifications@ema.europa.eu

This is an initiation by the European Commission of a procedure under Article 20 of Regulation (EC) No 726/2004

Common name(s):	**ivabradine**
Product Name(s):	**Procoralan / Corlentor**

Ivabradine was first authorised in the EU in October 2005. It is currently indicated for:

- symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm, either in patients 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.

- chronic heart failure NYHA II to IV class with systolic dysfunction, in patients with sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

The main pharmacodynamic property of ivabradine is a specific dose dependent reduction in heart rate. The usual recommended starting dose is 5 mg twice daily (2.5 mg if patient is over 75 years of age), which can be increased to 7.5 mg twice daily depending on therapeutic response.

On 30 April 2014, the EMA received a communication from the MAH on the preliminary results of the SIGNIFY study.

The SIGNIFY study 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 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 7.5 mg twice daily, up to 10 mg twice daily).

In the whole population (n=19102), ivabradine was not found to significantly affect the primary composite endpoint (PCE) or its individual components (cardiovascular deaths and non-fatal myocardial infarction). However, in the pre-specified subgroup of symptomatic angina patients (n=12049), a statistically significant increase in the 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 cardiovascular deaths and non-fatal myocardial infarction. These findings appear contradictory with findings from previous ivabradine studies in patients with coronary artery disease.

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 (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns and their impact on the benefit risk balance for the centrally authorised medicinal products Procoralan and Corlentor. The EC requests the Agency to give its opinion as soon as possible and not later than October on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn.

The Agency is also asked to consider and give an opinion on whether provisional measures are necessary to protect public health.

[redacted]

Sabine Jülicher
Head of Unit D5 Medicinal products – authorisations, European Medicines Agency
DG Health and Consumers

Date 8.05.2014