08 May 2014
EMA/PRAC/281252/2014

PRAC List of questions

To be addressed by the marketing authorisation holder for Corlentor and Procoralan

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

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

INN: ivabradine

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

The MAH is requested to provide the following in writing:

1. The MAH should provide an overview of the use of ivabradine in the EU, per Member State, including a breakdown by age group, by indication and by dose (2.5mg bid, 5mg bid, 7.5mg bid).
2. The MAH is requested to submit their analysis of the SIGNIFY study. An analysis of the interaction between key baseline characteristics (including severity of CCS class) and outcomes should be provided. In their analysis, the MAH should also address whether other patient characteristics can be identified that put patients at increased risk of major CV events (including the primary composite endpoint, CV death, fatal MI, non-fatal MI, and stroke), in particular patients who develop bradycardia (presented in categories, e.g. <45bpm, 45-50bpm, ….., 70-75 bpm, etc.), absolute heart rate, or reduction in heart rate achieved. Analyses stratified by dose should also be provided.
3. The MAH should provide an overview of changes in blood pressure and heart rate over time in the ivabradine and placebo groups in the pre-specified subgroup of symptomatic angina patients (CCS Class II or more) and discuss the impact on the PCE, CV death, and non-fatal MI. Time to achievement of the target heart rate and the occurrence of outcomes should be taken into account.
4. The MAH should provide the results on secondary endpoints, both in the pre-specified subgroup of symptomatic angina patients (CCS Class II or more) (n=12049) and in the randomized set (n=19102). The MAH should discuss whether any trends were observed;
5. The MAH is requested to provide an overview of the ivabradine doses (5mg bid, 7.5mg bid, 10mg bid) used, both for the pre-specified subgroup of symptomatic angina patients (CCS Class II or more) (n=12049) and the randomized set (n=19102).
6. The MAH is requested to discuss the apparent contradictory findings in symptomatic angina pectoris patients in the SIGNIFY and BEAUTIFUL trials.
7. The MAH is requested to discuss the impact of the results of the SIGNIFY study on the benefit – risk balance of ivabradine in the authorised indications in clinical practice.
8. Based on their evaluation of the benefit – risk balance of ivabradine, the MAH is requested to propose appropriate risk minimization measures, including changes to the SmPC/PL, and, if necessary, additional risk minimisation activities, which may improve the benefit-risk balance of ivabradine. Supportive justification should accompany each proposal which deviates from the risk minimisation measures already in place.
9. An updated RMP should be submitted, including proposals for additional pharmacovigilance activities to evaluate the effectiveness of risk minimisation.