Divergent Position

Procedure No: Corlentor EMEA/H/A20/1404/C/000598/0031
Procoralan EMEA/H/A20/1404/C/000597/0032

The undersigned members of CHMP did not agree with the CHMP's conclusions on the procedure under Article 20 of Regulation (EC) No 726/2004 EC for Procoralan/Corlentor. The reasons for divergent opinion were as follows:

Considering the target population and taking into account the clinical results of the SIGNIFY study, we consider the benefit-risk ratio of Procoralan/Corlentor negative in the indication symptomatic treatment of chronic stable angina pectoris in coronary artery disease patients for the following reasons:

1 - Ivabradine treatment did not demonstrate a beneficial effect on the primary composite endpoint (PCE) of cardiovascular death or non-fatal myocardial infarction: hazard ratio 1.08, 95% CI [0.96–1.20], p=0.197 (annual incidences of 3.03% vs 2.82%). Furthermore, in a pre-specified subgroup of symptomatic angina patients (CCS Class II or more) (n=12,049), a small but statistically significant increase in the PCE was observed with ivabradine: hazard ratio 1.18, 95% CI [1.03–1.35], p=0.018 (annual incidences of 3.37% vs 2.86%). Similar trends were observed with the components of the PCE, with non-statistically significant increases in the risks of cardiovascular deaths (hazard ratio 1.16, 95% CI [0.97–1.40], p=0.105, annual incidences of 1.76% vs. 1.51%) and non-fatal myocardial infarction (hazard ratio 1.18, 95% CI [0.97–1.42], p=0.092, annual incidences of 1.72% vs. 1.47%).

2 – The increased risk of atrial fibrillation.

3 – The risk of off-label use of Procoralan in patients with tachycardia without angina or in patients with atrial fibrillation, when ivabradine should not be regarded as an antiarrhythmic agent or a bradycardic agent for tachyarrythmias treatment/prevention.

4 – Furthermore, the concomitant use of ivabradine with verapamil or diltiazem is now contraindicated due to the risk of severe bradycardia with these drugs, when calcium-channel blockers should be the first or second line treatment with beta-blockers.

Overall, for these reasons, we consider that the benefit-risk ratio of Procoralan/Corlentor is negative in the symptomatic treatment of chronic stable angina pectoris. The appropriate recommendation in our opinion would be to limit the symptomatic treatment of CAD indication to second or third line after failure (or contraindication) of all other appropriate anti anginal agents (including calcium-channel blockers, beta-blockers, long-acting nitrates) and not only in case of intolerance or contra-indication to the use of beta-blockers or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose.

CHMP members expressing a divergent position:

Pierre Demolis (FR)	20 November 2014	Signature: .....
Dimitrios Kouvelas (EL)	20 November 2014	Signature: .....