

## **Ivabradine (Procoralan) - New contraindication and recommendations to minimise the risk of cardiovascular events and severe bradycardia**

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recently concluded its review of ivabradine (Procoralan) and has made recommendations aimed at reducing the risk of adverse cardiac effects, including myocardial infarction and bradycardia in patients being treated for symptomatic chronic stable angina in coronary artery disease. This review was initiated in May 2014 following preliminary results of the SIGNIFY<sup>1</sup> study and these preliminary results were communicated at that time via a Direct Healthcare Professional Communication (DHPC) and in the 62<sup>nd</sup> edition of the HPRA Drug Safety Newsletter.

The preliminary results showed a small but statistically significant increase in the combined risk of cardiovascular death and non-fatal myocardial infarction with ivabradine compared with placebo in a pre-specified subgroup of patients with symptomatic angina of CCS class II or more. Initial data indicated that the adverse cardiovascular outcomes may be mostly associated with a target heart rate below 60 beats per minute (bpm) however, further evaluation of the data from the SIGNIFY study was needed to fully understand its implications for the clinical use of ivabradine.

The final data from the SIGNIFY study<sup>2</sup> showed that in a subgroup of patients who had symptomatic angina, there was a small but significant increase in the combined risk of cardiovascular death or non-fatal myocardial infarction with ivabradine compared with placebo (3.4% vs. 2.9% yearly incidence rates). The data also indicated a higher risk of bradycardia with ivabradine compared with placebo (17.9% vs. 2.1%). Additional data assessed by the PRAC also showed that the risk of atrial fibrillation (AF) is increased in patients treated with ivabradine compared with controls (4.86% vs. 4.08%).

The benefit risk balance of ivabradine remains positive following review of the final data from the SIGNIFY study for its authorised indications\* however a small but significant increase of the combined risk of cardiovascular death, myocardial infarction and cardiac failure was seen in patients with symptomatic angina.

### **Advice to Healthcare Professionals:**

- The benefit-risk balance of Corlentor/Procoralan remains positive for its authorised indications.
- In the symptomatic treatment of patients with chronic stable angina, ivabradine is indicated in adults unable to tolerate, or with a contra-indication to the use of beta-blockers, or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose.
- Ivabradine is indicated for symptomatic treatment only, of chronic stable angina pectoris because ivabradine has no benefits on cardiovascular outcomes (e.g. myocardial infarction or cardiovascular death) in patients with symptomatic angina.
- Ivabradine is also indicated for treatment of chronic heart failure on the basis of results from the previous SHIFT study. The results of the SIGNIFY study do not impact on the heart failure indication.
- Concomitant use of ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is now contraindicated.
- Treatment with ivabradine should only be initiated in patients whose resting heart rate is at least 70 bpm.
- Prior to starting treatment with ivabradine or prior to dose titration, patients should be carefully monitored (serial heart rate measurements, E.C.G. or ambulatory 24-hour monitoring) for the occurrence of too low resting heart rates or symptoms of bradycardia.
- The risk of developing AF is increased in patients treated with ivabradine. Regular clinical monitoring for the signs and symptoms of AF is recommended and if AF develops, the balance of benefits and risks of continued treatment should be carefully considered.

- Treatment with ivabradine should be discontinued if the symptoms of angina do not improve within 3 months, or the improvement is limited and there is no clinically relevant reduction in resting heart rate within 3 months.
  - The usual recommended starting dose of ivabradine is 5 mg twice daily. The maintenance dose should not exceed 7.5 mg twice daily.
  - If the resting heart rate decreases persistently below 50 beats per minute or the patient experiences symptoms related to bradycardia, the ivabradine dose must be down-titrated, including the possible dose of 2.5 mg twice daily.
- The dose should only be increased to 7.5 mg twice daily after three to four weeks of treatment if the therapeutic response with 5 mg twice daily is insufficient and if the 5 mg dose is well tolerated. The effect of a dose increase on the heart rate should be carefully monitored.
- A Direct Healthcare Professional Communication (DHPC) outlining these recommendations has been circulated by the Marketing Authorisation Holder and is available from the HPRA website. The approved product information\* (Summary of Product Characteristics (SmPC)) and package leaflet (PL) will be updated accordingly.

### Key messages

- Ivabradine is indicated for symptomatic treatment only, of chronic stable angina pectoris because ivabradine has no benefits on cardiovascular outcomes (e.g. myocardial infarction or cardiovascular death) in patients with symptomatic angina.
- Serial heart rate measurements are required prior to initiation of therapy or prior to dose titration.
- Concomitant use of ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is now contraindicated.
- Treatment with ivabradine should only be initiated in patients whose resting heart rate is at least 70 bpm.
- Healthcare professionals should take note of the recommendations and relevant precautions in the product information for ivabradine, particularly in relation to dosing recommendations (not exceed the recommended daily dose of 7.5mg bd), maintenance of therapy, risk of developing AF, monitoring of and the potential impact of concomitant heart rate reducing effects of other medicines.

*\*Products currently authorised in Ireland include Procoralan. Further details of indications are available at [www.hpra.ie](http://www.hpra.ie) and [www.ema.europa.eu](http://www.ema.europa.eu)*

### References:

1. Study assessInG the morbi-mortality beNefits of the If inhibitor ivabradine in patients with coronary arterY disease.
2. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med* 2014; 371: 1091-9. Available at: <http://www.nejm.org/doi/full/10.1056/NEJMoa1406430>

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