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Direct Healthcare Professional Communication

Procoralan (ivabradine hydrochloride) - New contraindication and recommendations to minimise the risk of cardiovascular events and severe bradycardia

Dear Healthcare Professional,

Servier, in agreement with the European Medicines Agency and Health Products Regulatory Authority (HPRA), would like to inform you about new recommendations on the use of ivabradine in order to minimise the risk of cardiovascular events and severe bradycardia.

Summary of new advice:

- **In the symptomatic treatment of patients with chronic stable angina, ivabradine should only be started if the patient´s resting heart rate is above or equal to 70 beats per minute (bpm).**
- **Ivabradine should be discontinued if the symptoms of angina do not improve within 3 months.**
- **The concomitant use of ivabradine with verapamil or diltiazem is now contraindicated.**
- **Prior to treatment initiation or when considering titration, the heart rate should be monitored frequently, including serial heart rate measurements, ECG, or ambulatory 24-hour monitoring.**
- **The risk of developing atrial fibrillation is increased in patients treated with ivabradine. Regular clinical monitoring for the occurrence of atrial fibrillation is recommended. If atrial fibrillation develops during treatment, the balance of benefits and risks of continued ivabradine treatment should be carefully reconsidered.**

Prescribers are reminded that:

- **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.**
- **The starting dose of ivabradine should not exceed 5 mg twice daily.**
- **If the patient is still symptomatic after three to four weeks of treatment the dose may be increased to 7.5 mg twice daily if the initial dose is well tolerated and if resting heart rate remains above 60 bpm. The effect of a dose increase on the heart rate should be carefully monitored.**
- **The maintenance dose of ivabradine should not exceed 7.5 mg twice daily.**
- **If, during treatment, heart rate decreases below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward including the lowest dose of 2.5 mg twice daily. After dose reduction, heart rate should be monitored. Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist despite dose reduction.**

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Further information on the safety concern

The above recommendations are made following the evaluation of the results of the SIGNIFY study. This randomized placebo-controlled study was performed in 19,102 coronary artery disease patients without clinical heart failure.

Patients in the ivabradine group were started on a higher than recommended dose of 7.5 mg b.i.d. (5 mg b.i.d, if aged > 75 years) which was then titrated up to a maximum of 10 mg twice daily, which is higher than the recommended starting dose of 5 mg and a maximum dose of 7.5 mg twice daily.

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 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 risk of cardiovascular death (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%). There was no excess of sudden death in the ivabradine group, suggesting no ventricular proarrhythmic effect of ivabradine. The higher than approved dose used in the study did not fully explain these findings.

In the overall population, there was a significantly higher incidence of bradycardia (symptomatic and asymptomatic) with ivabradine than with placebo (17.9% vs. 2.1%), with more than 30% of the patients in the ivabradine group having their resting heart rate lowered, on at least one occasion, to below 50 bpm. Verapamil, diltiazem or strong CYP 3A4 inhibitors were received by 7.1% of patients during the study.
In the SIGNIFY study atrial fibrillation was observed in 5.3% of patients taking ivabradine compared to 3.8% in the placebo group. In a pooled analysis of all the Phase II/III double blind controlled clinical trials with a duration of at least 3 months including more than 40,000 patients, the incidence of atrial fibrillation was 4.86% in ivabradine treated patients compared to 4.08% in controls, corresponding to a hazard ratio of 1.26, 95% CI [1.15-1.39].

In addition to the recommendations above we would like to highlight that the product information will be updated with further information including the following:

- Ivabradine is indicated only for symptomatic treatment 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.

- Patients should be informed of signs and symptoms of atrial fibrillation and be advised to contact their physician if these occur.

- Discontinuation of treatment should be considered if there is only limited symptomatic response and no clinically relevant reduction in resting heart rate within 3 months.

Call for reporting
As a reminder, there is a need to report any suspected adverse reactions in accordance with the HPRA spontaneous reporting system. Suspected adverse reactions should be reported to the HPRA using a Yellow Card obtained either from the HPRA, or electronically via the website at www.hpra.ie. Adverse reactions can also be reported to the HPRA by calling (01) 676 4971.

Company contact point
For further inquiries concerning this information, please contact the Medical Information Department of SERVIER 01-6638110 and Medical and Regulatory Affairs Manager, Servier Laboratories, Block 2, West Pier Business Campus, Old Dunleary Road, Dun Laoghaire, Co. Dublin.

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